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CONFERENCE OVERVIEW

The field of vaccinology continues to expand and innovate 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. These achievements are moving the field forward, with the expectation that many current, challenging diseases – including chronic, non-infectious, and neoplastic – may become vaccine-preventable or vaccine-treatable in the near future.

The 19th Annual Conference on Vaccine Research provides high-quality, current reports of scientific progress and best practices featured in invited presentations, submitted oral presentations, and posters. The conference brings together the diverse disciplines involved in the research and development of vaccines and associated technologies for disease control through immunization. By drawing upon an international audience of scientists and researchers, healthcare professionals and trainees, veterinarians, vaccine manufacturers, and public health officials, the conference is designed to encourage the exchange of ideas across a broad range of disciplines.

The conference organizers invite you to participate as fully as possible in this exciting program, including interactive audience discussions, poster presentations, Dr. Richard J. Duma Meet the Experts breakfast session, Robert Austrian Memorial Lecture, and Dr. Charles Mérieux Award for Achievement in Vaccinology and Immunology and Maurice R. Hilleman Early-Stage Career Investigator Award presentations.

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: Towards a Universal Influenza Virus Vaccine
• List the currently used influenza virus vaccine platforms.

Symposium 1: Vaccine Introduction, Implementation, and Utilization
• Describe the need for annual revaccinations against influenza and not measles.
• Discuss how to design a long-lasting cross-protective universal influenza virus vaccine.

• Describe the spectrum of vaccine decision-making.
• Articulate the most common anti-vaccine arguments put forward to justify vaccine rejection, and provide data-driven answers to these objections.
• Explain the consequences of vaccine rejection.
• Describe the patient-centric elements of vaccine decision-making.
• Articulate the common cognitive styles and biases patients employ in making decisions about vaccines.
• Use the Preferred Cognitive Styles Model to assist patients in making decisions about vaccine acceptance.
• Explain what is meant by a systems approach to vaccine decision-making.
• Review the use of computational modeling to better understand vaccine systems.
• Describe the investigational new drug vaccine development regulatory process.

Symposium 2: Ebola: Lessons Learned
• Define groups at high risk for Ebola Virus Disease or serious complications.
• Review epidemiologic features of the West Africa Ebola outbreak.
• Communicate the activities led by World Health Organization to coordinate multiple consortia in expedited clinical evaluation of the two candidate Ebola vaccines that were most advanced as of August 2014.
• Review the efficacy trials performed and planned with three Ebola vaccine candidates in West Africa during the 2014-15 Ebola Viral Disease (EVD) outbreak.
• Explain Gavi's role in immunization, the 2015 Ebola outbreak, and its potential role in disease outbreaks going forward.

Keynote II: Mary Lou Clements-Mann Memorial Lecture in Vaccine Sciences: Systems Vaccinology: Probing the Human Immune System with Vaccines
• Explain how two recent developments might increase understanding on how vaccines stimulate the protective immune response.

Symposium 3: Emerging and Re-Emerging Diseases
• Discuss special considerations relevant to dengue vaccines, approaches being used to develop dengue vaccines, recent clinical experiences with leading candidates, and public health implications.
• List the basic components of high pathogenicity avian influenza (HPAI) control and eradication programs in the US and the world for the 39 HPAI poultry epizootics.
• Learn how vaccines can be used as a tool in HPAI control and eradication.
• Describe the practical biotechnologies used to develop the emergency vaccine bank for US poultry.
• Discuss current Zika virus vaccine candidates.
• Describe Zika virus vaccine target profiles.
• Explain the lessons learned from other flavivirus vaccine development efforts.
• Discuss the status of Chikungunya in the Americas.
• Review options for vaccine development, focusing on the virus-like particle (VLP) approach that is now in Phase II testing.

Symposium 4: HIV Vaccines and Passive Immunity
• Explain the new strategies currently being tested to elicit bnAbs by multiple vaccine candidates.
• Discuss the challenges using broadly neutralizing antibodies in HIV vaccine design.
• Discuss anti-HIV broadly neutralizing antibodies that are in clinical development, their potential applications in HIV treatment as adjuncts to standard antiretroviral therapy or as part of eradication strategies.
• Discuss the current options for passive and active immunization to prevent HIV infection, focusing on approaches based on protection through neutralizing antibody activity.

Symposium 5: Combatting Antimicrobial Resistance with Vaccines
• Explain what the expectations of the World Health Organisation for Animal Health (OIE) are regarding vaccine development.
• Discuss the impact that *H. influenzae* type b vaccine and *S. pneumoniae* vaccines have had on antibiotic resistance and review the progress towards a *S. aureus* vaccine.
• Explain how to search and discover bacterial polysaccharides and how to synthesize and characterize polysaccharide conjugate vaccines.
Symposium 6: Maternal Immunization

- Explain the concept of maternal immunization as a strategy to prevent infectious diseases in mothers and infants.
- Discuss the rationale and methodology associated with studying vaccines for administration during pregnancy.
- Review safety monitoring in maternal immunization studies sponsored by the Division of Microbiology and Infectious Disease at the National Institutes of Health, and how these efforts may align with the tools developed by the GAIA consortium.
- Discuss updates on recent National Vaccine Advisory Committee (NVAC) initiatives regarding maternal immunization.
- Discuss opportunities and challenges in the implementation of maternal immunization programs in limited-resource settings.
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This conference is supported, in part, through unrestricted educational grants from:

Dynavax  
EpiVax, Inc.  
Inovio Pharmaceuticals  
Merck & Co., Inc.  
Pfizer Inc.  
Sanofi Pasteur  
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NFID recognizes the following individuals for their support and contributions in planning this conference:

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*Subject to change

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As an organization accredited by the Accreditation Council for Continuing Medical Education (ACCME), the National Foundation for Infectious Diseases (NFID) must ensure balance, independence, objectivity, and scientific rigor in all its educational activities. NFID takes responsibility for the content, quality, and scientific integrity of this CME activity. All individuals in a position to control the content of an educational activity are required to disclose all relevant financial relationships with any ACCME-defined commercial interests for the past 12 months. Disclosure information is reviewed in advance to manage and resolve any real or perceived conflict of interest that may affect the balance and scientific integrity of an educational presentation. For details of NFID policies on managing conflicts of interest, visit www.nfid.org/coi.

- Wilbur Chen (Submitted Speaker) received grants for clinical research from PaxVax Inc.
- Ruth Carrico (Nurse Planner, Content Reviewer) owns stock or stock options from Merck & Co., Inc. and Pfizer Inc.; and served as a speaker for Pfizer Inc. and Sanofi Pasteur.
- Edgar Davidson (Submitted Speaker) is employed by Integral Molecular, Inc.
- Benjamin Doranz (Submitted Speaker) is employed by Integral Molecular, Inc.
- Lisa Dunkle (Submitted Speaker) is employed by and owns stock, stock options, or bonds in Protein Sciences Corporation.
- Marla Dalton (NFID Staff, Content Reviewer) owns stock, stock options, or bonds from Merck & Co., Inc.
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- Scott Halperin (Submitted Speaker) received grants for clinical research from GlaxoSmithKline and Sanofi Pasteur.
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- M. Anthony Moody (Invited Speaker) served as an advisor or consultant for GlaxoSmithKline; and owns, stock, stock options, or bonds from Cue Biologics.
- Peter Palese (Invited Speaker) received grants for clinical research from GlaxoSmithKline.
- Trish Perl (CPE Committee) served as an advisor or consultant for Hospira (Theradoc), and Pfizer Inc.; and received grants for clinical research from Merck & Co., Inc. and Sage.
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• **H. Keipp Talbot** (NFID CPE Committee, Content Reviewer) served as an advisor or consultant for TEVA Safety Board; and received grants for clinical research from Gilead, MedImmune, and Sanofi Pasteur.

• **Vincent Tam** (NFID CPE Committee) served as an advisor or consultant for Cubist and Tetraphase; received grants for clinical research from Rempex and Theravance; and served as speaker for Stendhal.

• **Hung Fu Tseng** (Submitted Speaker) received grants for clinical research from Novartis Vaccine.

• **Richard Zimmerman** (NFID CPE Committee and submitted speaker) received grants for clinical research from Merck & Co., Pfizer Inc., and Sanofi Pasteur.

All other faculty, activity planners/reviewers, and staff for this activity have no relevant financial relationships to disclose.
ACCREDITATION

CONTINUING MEDICAL EDUCATION (CME) CREDITS
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the National Foundation for Infectious Diseases (NFID). The National Foundation for Infectious Diseases is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The National Foundation for Infectious Diseases designates this educational activity for a maximum of 19.5 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CONFERENCE EVALUATION
For CME credit, visit www.meetingproceedings.com/NFID/ACVR16.htm to complete the conference evaluation and earn continuing education credits. You will need your registration confirmation number to access the online conference evaluation. The confirmation number can be found on your registration confirmation email and your conference badge. Following the conference, attendees will also receive a reminder email that includes the confirmation number. Emails will be sent to the email address used at the time of registration.

For additional assistance, please contact Ashley Cavell, NFID Education Coordinator, at acavell@nfid.org.

GENERAL INFORMATION

AMERICANS WITH DISABILITIES ACT
The Hyatt Regency Baltimore Inner Harbor is fully accessible to the public in accordance with the Americans with Disabilities Act guidelines. If you have any special meeting needs or requirements, please contact either NFID or hotel staff.

CONFERENCE REGISTRATION DESK
The conference registration desk is located in the Constellation Ballroom Foyer in the hotel. 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 Baltimore Inner Harbor
300 Light Street
Baltimore, MD 21202
410-528-1234

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 and using environmentally friendly ink. To reduce the amount of paper used, presentations will be made available online.
• Encouraging attendees to reduce, reuse, and recycle paper, metal, plastic, and glass.
• Providing a badge recycling box at the Conference Information Desk.
• Using reusable service wear such as cups, mugs, plates, and cutlery when possible.
• Encouraging attendees to turn off lights and other electronics when not in use and to
participate in the hotel’s linen reuse program for towels and bed linens.
• Encouraging attendees to walk around town or explore the area using local transportation.

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 NFID staff at the Conference Information Desk in the area outside of the Constellation Ballroom Foyer.

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

POSTER SESSION HOURS
Posters will be on display from 5:00 PM on Monday, April 18 until 12:00 PM on Wednesday, April 20 in the Atrium of the hotel. Presenters will be at their boards to answer questions and discuss their research during the poster reception scheduled for Monday, April 18, at 5:00–6:00 PM and during the poster session on Tuesday, April 19, at 7:30–8:30 AM.

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

PROGRAM BOOK AND ABSTRACTS
The registration fee includes one copy of the Program Agenda and Abstract Book for each registered attendee. Additional copies, if available, may be purchased onsite at the conference registration desk beginning on Wednesday, April 20.

PLEASE NOTE THAT NFID IS UNABLE TO REPLACE LOST PROGRAM BOOKS.

REGISTRATION FEE AND HOURS
Space is limited and onsite registrations will be accepted on a first-come, first-served basis.

The full registration fee includes one copy of the program agenda and abstract book, continental breakfasts, all scheduled coffee breaks, welcome reception on Monday evening, and luncheon on Tuesday. Accommodations and additional meals are not included.

The registration desk will be open:
• Sunday, April 17, 4:30–6:30 PM
• Monday, April 18, 7:30 AM–5:00 PM
• Tuesday, April 19, 7:00 AM–5:00 PM
• Wednesday, April 20, 7:00 AM–3:30 PM
DR. RICHARD J. DUMA MEET THE EXPERTS BREAKFAST SESSION

Named in honor of NFID founder, Richard J. Duma, MD, PhD, the Meet the Experts Breakfast Session is conducted in a small group format focused 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 session is open to all attendees. Please be sure to take advantage of this networking opportunity for a thoughtful exchange of ideas among peers, mentors, and colleagues.

The Dr. Richard J. Duma Meet the Experts Breakfast Session is scheduled for Wednesday, April 20 from 7:00-7:45 AM, in the Constellation Ballroom C.

Wednesday, April 20

Pre-Clinical Early Evaluation of Viral Vaccines
Hana Golding, PhD

Maternal Immunization
Flor Munoz-Rivas, MD

Vaccines for the Global Community
Kathleen M. Neuzil, MD, MPH

What Causes Vaccine-Hesitancy?
Gregory A. Poland, MD

Flaviviruses
COL Stephen J. Thomas, MD
19th annual conference on Vaccine Research

NFID Luncheon
Tuesday, April 19, 2016
12:30–1:45 PM
Opening Remarks and Introductions

Robert Austrian Memorial Lecture
Daniel M. Musher, MD

Presentation of Dr. Charles Mérieux Award for Achievement in Vaccinology and Immunology

Dr. Charles Mérieux Award Acceptance
Kathryn M. Edwards, MD

Presentation of Maurice R. Hilleman Early-Stage Career Investigator Award
(Recipient to be announced)

---

Daniel M. Musher, MD
2016 Robert Austrian Memorial Lecturer
*Distinguished Service Professor, Department of Medicine, Baylor College of Medicine*

Dr. Daniel Musher is a Distinguished Service Professor of Medicine and Professor of Molecular Virology and Microbiology at the Baylor College of Medicine and has been on staff at the VA Medical Center Houston since 1971. He has worked in the classical triad of clinical medicine, teaching, and research. His research has focused on bacterial infections, principally those due to *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, and *Treponema pallidum*. He is the coauthor of 520 papers and chapters including many on immune responses to pneumococcal antigens.

---

Kathryn M. Edwards, MD
2016 Dr. Charles Mérieux for Achievement in Vaccinology and Immunology Award Recipient
*Sarah H. Sell and Cornelius Vanderbilt Chair in Pediatrics*
*Director, Vanderbilt Vaccine Research Program*
*Vanderbilt University School of Medicine*

Dr. Edwards is the Sarah H. Sell and Cornelius Vanderbilt Professor of Pediatrics and directs the Vanderbilt Vaccine Research Program. She graduated from the University of Iowa College of Medicine and completed her pediatric residency and infectious disease fellowship at Northwestern University and her postdoctoral training in Immunology at Rush Medical School in Chicago. Dr. Edwards joined the Vanderbilt Vaccine Program in 1980 and has conducted many pivotal vaccine studies since that time. She has had extensive experience in leading NIH-funded multicenter initiatives; in designing, conducting, and analyzing pivotal Phase I, II, and III clinical studies on vaccines and therapeutics; in facilitating networking with basic and clinical investigators with a wide range of interests and expertise; and in mentoring many of the young investigators who currently work within the research unit.
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 for Achievement in Vaccinology and Immunology

The Dr. Charles Mérieux Award for Achievement in Vaccinology and Immunology honors individuals whose outstanding lifetime contributions to the fight against vaccine-preventable diseases have led to significant improvement in public health. The award is named for Dr. Charles Mérieux, the distinguished French scientist who devoted his life to fighting infectious diseases globally, combining his medical knowledge with an understanding of business to develop one of the world’s leading vaccine laboratories, the Pasteur Institute. Dr. Mérieux was also a founder of the French Institute of Foot-and-Mouth Disease (later renamed the Mérieux Institute), and used in-vitro cultivation to produce millions of doses of vaccines. First offered in 2005, the award is presented annually at the Annual Conference on Vaccine Research.

Maurice R. Hilleman Early-Stage Career Investigator Award

The Maurice R. Hilleman Early-Stage Career Investigator Award memorializes the lifetime achievements of Dr. Maurice R. Hilleman in the field of vaccinology. Dr. Hilleman was a long-serving member of the National Foundation for Infectious Diseases (NFID) Board of Directors and Board of Trustees and was the 1998 recipient of the NFID 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. The award provides $10,000 to support research activities at the awardee’s institution, as well as a travel stipend and complimentary registration to attend the following year’s Annual Conference on Vaccine Research.
MARY LOU CLEMENTS-MANN MEMORIAL LECTURE IN VACCINE SCIENCES

Bali Pulendran PhD, Charles Howard Candler Professor of Pathology and Laboratory Medicine, Emory University, will present the 2016 Mary Lou Clements-Mann Memorial Lecture, “Systems Vaccinology: Probing the Human Immune System with Vaccines” on Tuesday, April 19, 2016 at 8:30 AM.

Abstracts start on page 54

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 Johns 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 the development process forward.

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 advocate for 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.
SUNDAY, APRIL 17, 2016

4:30–6:30 PM  Registration  Constellation Ballroom Foyer

MONDAY, APRIL 18, 2016

7:30 AM–5:00 PM  Registration  Constellation Ballroom Foyer

7:30 AM  Poster Set–Up  Atrium

7:45-8:15 AM  Continental Breakfast  Constellation Ballroom Foyer and Atrium

8:15 AM  Welcome and Introductions
William Schaffner, MD
National Foundation for Infectious Diseases
Bethesda, MD

Keynote I:  
Moderator:  Kathleen M. Neuzil, MD, MPH
Center for Vaccine Development
University of Maryland School of Medicine
Baltimore, MD

8:30 AM  1  Towards a Universal Influenza Virus Vaccine
Peter Palese, PhD
Icahn School of Medicine at Mount Sinai
New York, NY

9:15 AM  Questions and Answers

9:30 AM  Coffee Break

Symposium 1:  
Vaccine Introduction, Implementation, and Utilization  
Moderator:  Gregory A. Poland, MD
Edward Jenner Society
Mayo Clinic and Foundation
Rochester, MN

9:45 AM  2  The Spectrum of Vaccine Resistance:  Why Are They Hesitant?
Gregory A. Poland, MD
Edward Jenner Society
Mayo Clinic and Foundation
Rochester, MN
<table>
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<tr>
<th>Time</th>
<th>Session</th>
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</table>
Caroline M. Poland, MA, LMHC, LCAC, NCC  
Taylor University  
Upland, IN |
| 10:35 AM | 4  Vaccine Economics and Utilization  
Bruce Y. Lee, MD, MBA  
Johns Hopkins Bloomberg School of Public Health  
Baltimore, MD |
| 11:00 AM | 5  Getting Your Vaccine to Market: A Regulatory Perspective  
Cara Fiore, PhD  
Center for Biologics Evaluation and Research  
US Food and Drug Administration  
Bethesda, MD |
| 11:30 AM | Questions and Answers |
| 12:00 PM | Lunch (on your own) |
|          | **Symposium 2:**  Ebola: Lessons Learned  
Moderator:  Myron M. Levine, MD, DTPH  
Global Health, Vaccinology & Infectious Diseases  
University of Maryland School of Medicine  
Baltimore, MD |
| 1:00 PM  | 6  Who Needs an Ebola Vaccine: Epidemiology and Target Populations Revisited  
RADM Anne Schuchat, MD  
Centers for Disease Control and Prevention  
Atlanta, GA |
| 1:30 PM  | 7  Rapid Assembly of Consortia for Expeditious Testing of Ebola Vaccines  
Vasee Moorthy, PhD  
World Health Organization (WHO)  
Geneva, Switzerland |
| 2:00 PM  | 8  Efficacy Trials in West Africa  
John-Arne Røttingen, MD, PhD  
Norwegian Institute of Public Health  
Oslo, Norway |
| 2:30 PM  | 9  Ebola Vaccine: Gavi Perspectives  
Jon Pearman, MSc  
Gavi  
Geneva, Switzerland |
| 3:00 PM  | Coffee Break |
Submitted Presentations 1A:  

(Concurrent Sessions)  

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

3:30 PM  
S1 The Safety and Immunogenicity of a Parenterally Administered Modified Recombinant Staphylococcal Enterotoxin B Protein Vaccine  
J. Aman¹, W. H. Chen², R. Douglas¹, N. Greenberg², F. Holtsberg³, G. Liao¹, M. Pasetti², M. Reymann², X. Wang¹, K. Warfield¹  
¹Integrated BioTherapeutics, Inc., Gaithersburg, MD; ²Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, MD; ³Unither Virology, LLC, Silver Spring, MD

3:45 PM  
S2 Phase III Trial of Two Doses of Investigational Vaccine HEPLISAV-B™ Compared with Three Doses of Licensed Hepatitis B Vaccine ENGERIX-B® in Adults 18-70 Years of Age  
L. Akella, S. Jackson, R. Janssen, K. Jones  
Dynavax Technologies, Berkeley, CA

4:00 PM  
S3 Safety and Immunogenicity of H7 Influenza Prime-Boost Regimens in Healthy Adults  
A. DeZure², E. Coates², Z. Hu⁴, G. Yamshchikov⁷, K. Zephir², S. Plummer⁵, J. J. Gordon³, R. T. Bailer¹, X. Sun⁶, T. Tumpey⁶, B. Graham², J. Ledgerwood²  
¹NIH/NIAID/Vaccine Research Center, Gaithersburg, MD; ²NIH, Bethesda, MD; ³National Institutes of Health/Vaccine Research Center, Springdale, MD; ⁴National Institutes of Health, Rockville, MD; ⁵NIH/NIAID/National Institutes of Health, Clarksburg, MD; ⁶CDC, Atlanta, GA; ⁷NIH/NIAID/VRC, Bethesda, MD

4:15 PM  
S4 Efficacy of Recombinant Influenza Vaccine (Flublok® Quadrivalent, RIV4) versus Egg-Derived Inactivated Vaccine (IIV4) in Adults ≥50 During a Season Characterized by Antigenic Mismatch between Circulating and Vaccine H3N2 Strains  
M. Cox¹, L. M. Dunkle¹, K. L. Goldenhal², R. Izikson¹, D. Muse³, P. A. Patriarca⁴  
¹Protein Sciences Corporation, Meriden, CT; ²Bethesda Biologics Consulting, San Antonio, TX; ³Jean Brown Research Center, Salt Lake City, UT; ⁴Biologics Consulting Group, Inc., Alexandria, VA

4:30 PM  
S5 Safety and Immunogenicity of Tetanus-Diphtheria-Acellular Pertussis Vaccine (Tdap) During Pregnancy  
Dalhousie University, Halifax, Nova Scotia, Canada

4:45 PM  
S6 GEN-003, a Therapeutic Vaccine for Genital Herpes, Significantly Reduces Anogenital Lesion Rates and Mucosal HSV-2 Shedding  
J. Flechtner, S. Hetherington, S. Tasker  
Genocea Biosciences, Cambridge, MA
<table>
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<tr>
<th>Time</th>
<th>Session</th>
<th>Title</th>
<th>Presenters</th>
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<tr>
<td>3:30 PM</td>
<td>S7</td>
<td>Adverse Events Following DTaP Vaccination in the Vaccine Adverse Event Reporting System</td>
<td>P. L. Moro, P. Lewis, M. Cano&lt;br&gt;Centers for Disease Control and Prevention, Atlanta, GA</td>
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<tr>
<td>3:45 PM</td>
<td>S8</td>
<td>Surveillance of Adverse Events Following Immunization with Influenza Vaccines in Canada, 2012-15</td>
<td>N. Ahmadipour, C. Bancej, M. Gendron, J. Nkanza, R. Pless&lt;br&gt;Public Health Agency of Canada, Ottawa, Ontario, Canada</td>
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<tr>
<td>4:00 PM</td>
<td>S9</td>
<td>Assessing the Feasibility of Monitoring Influenza Vaccine Safety in Pregnant Women Using Text Messaging</td>
<td>K. R. Broder¹, A. Barrett³, M. Cano², P. Castaño⁴, O. A. Castellanos⁵, C. Gyamfi-Bannerman², K. Jakob², P. LaRussa², P. Lewis¹, O. I. Museru², M. S. Stockwell⁶&lt;br&gt;¹Centers for Disease Control and Prevention, Atlanta, GA; ²Columbia University, New York, NY; ³Columbia University Medical Center, New York, NY</td>
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<tr>
<td>4:30 PM</td>
<td>S11</td>
<td>Cases of Postural Orthostatic Tachycardia Syndrome (POTS) Reported to the Vaccine Adverse Event Reporting System (VAERS) Following Human Papillomavirus (HPV) Vaccination, June 1, 2006 – September 1, 2015</td>
<td>J. Arana¹, M. Cano¹, A. Mba-Jonas², C. Jankosky²&lt;br&gt;¹Centers for Disease Control and Prevention, Atlanta, GA; ²US Food and Drug Administration, Silver Spring, MD</td>
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<tr>
<td>4:45 PM</td>
<td>S12</td>
<td>A Post-Licensure Observational Study to Assess the Safety of a Meningococcal Conjugate Vaccine in Subjects 11-21 Years of Age</td>
<td>H. Tseng¹, L. Sy³, B. Ackerson¹, R. Hechter¹, S. Tartof⁶, DM. Haag⁶, J. Slezak³, Y. Luo³, C. Fischetti³, H. Takhar³, Y. Miao⁶, M. Cunnington³, Z. Solano³, S. Jacobsen³&lt;br&gt;¹Pediatrics and Pediatric Infectious Diseases, Southern California Permanente Medical Group, Harbor City, CA; ²GlaxoSmithKline plc, London United Kingdom; ³Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA; ⁴Seqirus BV, Amsterdam, the Netherlands; ⁵GlaxoSmithKline B.V., Amsterdam, the Netherlands</td>
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<td>5:00–6:00 PM</td>
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<td>Welcome Reception &amp; Poster Presentation</td>
<td>Atrium</td>
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TUESDAY, APRIL 19, 2016

7:00 AM–5:00 PM Registration Constellation Ballroom Foyer

7:30–8:30 AM Poster Presentation Breakfast Constellation Ballroom Foyer and Atrium

Keynote II: Mary Lou Clements-Mann Memorial Lecture in Vaccine Sciences

Moderator: Alison C. Mawle, PhD
Centers for Disease Control and Prevention
Atlanta, GA

8:30 AM 10 Systems Vaccinology: Probing the Human Immune System with Vaccines
Bali Pulendran, PhD
Emory Vaccine Center
Emory University
Atlanta, GA

9:15 AM Questions and Answers

9:30 AM Coffee Break

Symposium 3: Emerging and Re-Emerging Diseases

Moderator: Cristina G. Cassetti, PhD
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

9:45 AM 11 Update on Dengue Vaccines
Aravinda de Silva, PhD
University of North Carolina School of Medicine
Chapel Hill, NC

10:15 AM 12 Application of Biotechnology in Emergency Poultry Vaccines for Highly Pathogenic Avian Influenza
David E. Swayne, DVM, PhD
US National Poultry Research Center
Agricultural Research Services
US Department of Agriculture
Athens, GA

10:45 AM 13 Zika Vaccine Development
COL Paul B. Keiser, MD
Walter Reed Army Institute of Research
Silver Spring, MD
<table>
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<th>Time</th>
<th>Session</th>
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<tr>
<td>11:15 AM</td>
<td>Chikunguya Vaccine Development</td>
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<td>Barney S. Graham, MD, PhD</td>
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<td>National Institute of Allergy and Infectious Diseases</td>
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<td>National Institutes of Health</td>
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<td>Bethesda, MD</td>
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<td>11:45 AM-12:15 PM</td>
<td>Questions and Answers</td>
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<td>12:30 PM</td>
<td><strong>NFID Luncheon</strong></td>
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<td>Constellation Ballroom A &amp; B</td>
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<td>Robert Austrian Memorial Lecture</td>
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<td>Dr. Charles Mérieux Award Presentation</td>
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<td>Maurice R. Hilleman Early-Stage Career Investigator Award Presentation</td>
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<td>12:30 PM</td>
<td>Symposium 4: HIV Vaccines and Passive Immunity</td>
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<td>Constellation Ballroom A &amp; B</td>
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<td>Moderator: Hana Golding, PhD</td>
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<td>Center for Biologics in Evaluation and Research</td>
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<td>US Food and Drug Administration</td>
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<td>Rockville, MD</td>
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<td>1:45 PM</td>
<td>Pathways of Induction of HIV Broadly Neutralizing Antibodies</td>
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<td>M. Anthony Moody, MD</td>
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<td>Duke Human Vaccine Institute</td>
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<td>Duke University Medical Center</td>
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<td>Durham, NC</td>
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<td>2:10 PM</td>
<td>Broadly Neutralizing Antibodies and HIV Vaccine Design</td>
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<td>Dennis Burton, PhD</td>
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<td>Scripps Research Institute</td>
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<td>La Jolla, CA</td>
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<td>2:35 PM</td>
<td>Broadly Neutralizing Antibodies for Treatment of HIV Infected Patients</td>
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<td>Marina Caskey, MD</td>
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<td>The Rockefeller University</td>
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<td>New York, NY</td>
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<td>3:00 PM</td>
<td>Broadly Neutralizing mAbs and Antigens for HIV</td>
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<td>Barney S. Graham, MD, PhD</td>
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<td>National Institute of Allergy and Infectious Diseases</td>
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<td>National Institutes of Health</td>
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<td>Bethesda, MD</td>
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<td>3:25 PM</td>
<td>Questions and Answers</td>
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<td>3:45 PM</td>
<td><strong>Coffee Break</strong></td>
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</tbody>
</table>
Submitted Presentations 2A:  
**Constitution Ballroom A**

(Concurrent Sessions)  
**Moderator:** Richard J. Duma, MD, PhD  
Halifax Medical Center  
Daytona Beach, FL

4:15 PM  
**S13**  
*Generation of Inactivated Influenza Virus Vaccines Using Low-Energy Electron Irradiation*  
J. Fertey¹, T. Grunwald¹, E. Hiller², A. Pohl³, S. Rupp³, S. Ulbert¹, C. Wetzel³, L. Wierich¹  
¹Fraunhofer Institute for Cell Therapy and Immunology, Leipzig, Germany; ²Fraunhofer Institute for Interfacial Engineering and Biotechnology, Stuttgart, Germany; ³Fraunhofer Institute for Organic Electronics, Electron Beam and Plasma Technology, Dresden, Germany

4:30 PM  
**S14**  
*What Is Pneu with Pneumococcal Disease in Children in the Conjugate Vaccine Era*  
S. L. Deeks, J. Fediurek, J. B. Gubbay, M. Policarpio, S. Wilson, K. Wong  
Public Health Ontario, Toronto, Ontario, Canada

4:45 PM  
**S15**  
*Those Who Cannot Remember the Past Are Condemned to Repeat It (Santayana). Growing up Before Vaccines*  
E. F. Boudreau¹, C. H. Hoke, Jr.²  
¹Children of Uganda, Columbia, MD; ²Self Employed, Columbia, MD

5:00 PM  
**S16**  
*Decline of Maternal Measles Antibodies in Infants in Tianjin, China*  
M. Boulton¹, B. Carlson¹, J. Montgomery¹, A. L. Wagner¹, X. Wang², Y. Zhang²  
¹University of Michigan School of Public Health, Ann Arbor, MI; ²Tianjin Centers for Disease Control and Prevention, Tianjin, China

5:15 PM  
**S17**  
*Using the 4 Pillars™ Immunization Toolkit to Increase Adult Immunizations*  
M. Hawk¹, C. Lin², D. B. Middleton³, K. K. Moehling², M. Nowalk², J. M. Raviotta¹, E. Ricci², S. Zhang³, R. Zimmerman²  
¹University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA; ²University of Pittsburgh School of Medicine, Pittsburgh, PA; ³University of Pittsburgh School of Public Health, Pittsburgh, PA

Submitted Presentations 2B:  
**Constitution Ballroom B**

(Concurrent Sessions)  
**Moderator:** Hana Golding, PhD

4:15 PM  
**S18**  
*Viral Quasispecies Population Structure of Structural and Non-Structural Asibi/17D Chimeric Yellow Fever Virus*  
A. Barrett¹, A. Beck¹, N. Collins¹, S. Higgs²  
¹University of Texas Medical Branch, Galveston, TX; ²Kansas State University, Manhattan, KS

4:30 PM  
**S19**  
*RSV Assay Strengthening Work to Advance Vaccine Development*  
N. Hosken¹, J. J. Donnelly¹, B. D. Plikaytis¹, K. Mahmood¹, C. Trujillo¹, D. Higgins¹  
¹PATH, Seattle, WA; ²BioStat Consulting, LLC, Jasper, GA
4:45 PM  S20  A Replication Defective Human Cytomegalovirus (CMV) Vaccine  
   T. Fu  
   Merck and Co., Inc., West Point, PA  
5:00 PM  S21  RSV Infection & Vaccines: Antigenic Fingerprinting Following RSV Vaccination  
   and Infection Identify Novel Vaccine Targets  
   S. Fuentes, H. Golding, S. Khurana  
   US Food and Drug Administration, Silver Spring, MD  
5:15 PM  S22  Enhanced H7N9 Vaccine Immunogenicity Engineered by Regulatory T Cell  
   Epitope Deletion in Hemagglutinin  
   M. Ato¹, R. Chan², A. De Groot³, R. Liu⁴, B. C. Lefoley⁵, W. Martin⁶, L. Moise⁷,  
   A. Nithichanon⁶, T. M. Ross⁷, Y. Takahashi¹  
   ¹National Institute of Infectious Diseases, Tokyo, Japan;  
   ²Dr. Ted Ross, Coquitlam, British Columbia, Canada;  
   ³EpiVax, Inc., Providence, RI; ⁴Institute for Immunology and  
   Informatics - University of Rhode Island, Providence, RI; ⁵Ted Ross,  
   Athens, GA; ⁶Khon Kaen University, Khon Kaen, Thailand; ⁷University of  
   Georgia, Athens, GA

WEDNESDAY, APRIL 20, 2016

7:00 AM–3:30 PM  Registration  
   Constellation Ballroom Foyer

7:00–7:45 AM  Dr. Richard J. Duma Meet the Experts Breakfast Session  
   Constellation Ballroom C

Pre-Clinical Early Evaluation of Viral Vaccines  
   Hana Golding, PhD  
   Center for Biologics Evaluation and Research  
   US Food and Drug Administration  
   Rockville, MD

Maternal Immunization  
   Flor Munoz-Rivas, MD  
   Baylor College of Medicine  
   Houston, TX

Vaccines for the Global Community  
   Kathleen M. Neuzil, MD, MPH  
   University of Maryland School of Medicine  
   Baltimore, MD
Why Are People Vaccine Hesitant?
Gregory A. Poland, MD
Edward Jenner Society
Mayo Clinic and Foundation
Rochester, MN

Flaviviruses
COL Stephen J. Thomas, MD
Walter Reed Army Institute of Research
Silver Spring, MD

7:30-8:00 AM       Continental Breakfast
Constellation Ballroom Foyer

Submitted Presentations 3A:  
(Concurrent Sessions) Moderator: Alison C. Mawle, PhD
Centers for Disease Control and Prevention
Atlanta, GA

8:00 AM            S23 Testing the Effect of a Novel Glycolipid-Based Adjuvant for a Human Malaria Vaccine in Human Immune System (HIS) Mice
M. Tsuji
Aaron Diamond AIDS Research Center, Affiliate of the Rockefeller University,
New York, NY

8:15 AM            S24 Comprehensive Mutagenesis of Dengue Virus Envelope Proteins to Map Antibody Epitopes and Functional Regions
E. Christian, E. Davidson, B. Doranz, J. Pfaff
Integral Molecular, Inc., Philadelphia, PA

8:30 AM            S25 Identification of Aim2 as a Mediator for Alum’s Adjuvant Effects
D. Farfan, K. Fitzgerald, S. Lu, J. Suschak, S. Wang
University of Massachusetts Medical School, Worcester, MA

8:45 AM            S26 Aerosolized Ebola Vaccine Elicits Robust Antibody and Lung-Resident T cell Responses and Protects Non-Human Primates against Virus Challenge
A. Bukreyev1, P. Collins1, T. Garron1, K. Fenton1, T. Geisbert1, C. Klages1,
N. Lubaki1, M. Meyer1, C. Mire1, G. Olinger3
1University of Texas Medical Branch at Galveston, Galveston, TX;
2National Institute of Allergy and Infectious Diseases/National Institutes of Health, Bethesda, MD;

9:00 AM            S27 Ebola Infection and Vaccines: Novel Tools for Better Understanding of Antibody Immune Responses Identifies Novel Potential Protective Targets
E. Coyle, S. Fuentes, S. Khurana, S. Ravichandran
US Food and Drug Administration, Silver Spring, MD
9:15 AM  

S28  

Mapping Antibody Epitopes on the Ebola Virus Envelope Protein by Shotgun Mutagenesis  
T. Barnes¹, C. Bryan¹, J. Crowe, Jr.², E. Davidson³, B. Doranz¹, A. Flyak², R. Fong¹  
¹Integral Molecular, Inc., Philadelphia, PA; ²Vanderbilt University, Nashville, TN

Submitted Presentations 3B:  

(Concurrent Sessions)  

Moderator:  Raphael Simon, PhD  
University of Maryland School of Medicine  
Baltimore, MD

8:00 AM  S29  

A Genome-Wide Association Study Identifies Major Loci Associated with Measles Vaccine-Specific Immune Responses  
I. H. Haralambieva, R. B. Kennedy, B. R. Larrabee, I. G. Ovsyannikova, G. A. Poland, D. J. Schaid  
Mayo Clinic, Rochester, MN

8:15 AM  S30  

Immunization of Rabbits with Epstein-Barr Virus (EBV) gH/gL and gB Recombinant Proteins Elicits Higher EBV-Neutralizing Antibody Titers Than Those Induced by EBV gp350  
Z. Cao, Q. Chen, X. Cui, C. M. Snapper  
Uniformed Services University of the Health Sciences, Bethesda, MD

8:30 AM  S31  

Multivalent PRINT® Nanoparticulate Pneumococcal Vaccines: Polysaccharide Protein Vaccines Stimulate Robust B and T Cell Immune Response  
A. L. Galloway, M. R. Stone  
Liquidia Technologies, Research Triangle Park, NC

8:45 AM  S32  

Strong, But Age-Dependent, Protection Elicited by a 2nd Generation DNA/Modified Vaccinia Ankara Simian Immunodeficiency Virus Vaccine  
R. Amara¹, H. Balachandran², R. Basu³, V. Chamcha¹, S. Kannanganat⁴, P. A. Kozlowski⁵, D. C. Montefiori⁶, B. Moss⁷, H. L. Robinson⁸, S. Sahu¹, S. Santra⁸  
¹Emory University, Atlanta, GA; ²Beth Israel Deaconess Medical Center, Boston, MA; ³GeoVax, Inc., Smyrna, GA; ⁴Houston Methodist, Houston, TX; ⁵Louisiana State University Health Sciences Center, New Orleans, LA; ⁶Duke University Medical Center, Durham, NC; ⁷National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD; ⁸Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

9:00 AM  S33  

Live Imaging Animal Model of RSV for Evaluation of Vaccines and Therapeutics  
D. Arenas¹, S. Fuentes¹, H. Golding¹, S. Khurana¹, M. Moore²  
¹US Food and Drug Administration, Silver Spring, MD; ²Emory University, Atlanta, GA
19th annual conference on Vaccine Research

9:15 AM
S34 Co-Delivery of Antigens Using a Novel Nanoparticle Pneumococcal Vaccine Induce Enhanced Immunogenicity in the Absence of Adjuvants
M. Earl, M. R. Stone
Liquidia Technologies, Research Triangle Park, NC

9:30 AM
Coffee Break

Symposium 5: Combating Antimicrobial Resistance with Vaccines
Moderator: Cyril G. Gay, DVM, PhD
Agricultural Research Service
US Department of Agriculture
Beltsville, MD

10:00 AM
19 Prioritization of Diseases for Which Vaccines Could Reduce Antimicrobial Use in Animals
Elisabeth Erlacher-Vindel, PhD
World Organisation for Animal Health (OIE)
Paris, France

10:30 AM
20 Vaccines As a Tool to Diminish Antibiotic Resistance: The Example of a S. aureus Vaccine
Robert S. Daum, MD, CM
The University of Chicago
Chicago, IL

11:00 AM
21 Development of Vaccines to Prevent Clostridium difficile and Campylobacter jejuni Infections
Mario A. Monteiro, PhD
University of Guelph
Guelph, ON
Canada

11:30 AM
Questions and Answers

12:00 PM
Lunch (on your own)

Symposium 6: Maternal Immunization
Moderator: Marion F. Gruber, PhD
Center for Biologics in Evaluation and Research
US Food and Drug Administration
Rockville, MD

1:00 PM
22 Clinical Trials of Vaccines Administered During Pregnancy
Flor Munoz-Rivas, MD
Baylor College of Medicine
Houston, TX
1:25 PM 23 Safety Monitoring in Immunization in Pregnancy Efforts at NIH
Richard L. Gorman, MD
National Institute of Allergy and Infectious Diseases
Bethesda, MD

1:50 PM 24 NVAC Initiatives
Saad B. Omer, MBBS, MPH, PhD
Emory University
Atlanta, GA

2:15 PM 25 Maternal Immunization: Perspective of PATH
Niranjan Bhat, MD, MHS
PATH
Seattle, WA

2:40 PM 26 Regulatory Perspectives
Marion F. Gruber, PhD

3:05 PM Questions and Answers

Closing Session: Combating Antimicrobial Resistance: Vaccines in the Pipeline
Moderator: Bruce Gellin, MD, MPH
National Vaccine Program Office
US Department of Health and Human Services
Washington, DC

3:30 PM Panel Discussion on Combating Antimicrobial Resistance: Vaccines in the Pipeline
Tim Cooke, PhD
NovaDigm Therapeutics

Kent Kester, MD
Sanofi Pasteur

Charles Knirsch, MD, MPH
Pfizer

Lewis Schrager, MD
Aeras

5:00 PM Adjourn
POSTER SESSIONS
P1 A Liposomal Formulation of NOD1 and NOD2 Agonists Reduces Lung Bacterial Burden in BCG-Primed CB6F1 Mice Challenged with *Mycobacterium tuberculosis*

J. Schaeffer¹, M. Breiner², A. Hogg³, Q. Xia³, D. Duso³, W. W. Reiley³, D. Laddy³

¹Aeras, Rockville, MD; ²Emergent Biosolutions, Gaithersburg, MD; ³Trudeau Institute, Inc., Saranac Lake, NY

P2 GPI-Anchored CCL28 as a Strong Mucosal Immunostimulator with Influenza VLPs

R. W. Compans, T. Mohan, B. Wang

Emory University, Atlanta, GA

P3 Characterization of N-peptide Fusion Inhibitor Resistance Pathways

C. J. De Feo¹, M. Hsieh², P. W. Keller¹, R. Vassell¹, W. Wang¹, C. D. Weiss¹

¹US Food and Drug Administration, Silver Spring, MD; ²US Food and Drug Administration, Lansing, MI

P4 Design and Characterization of Bacterially Expressed Hemagglutinin Head Domain Immunogens

S. Swaroop, V. Mallajosyula, R. Varadarajan

Indian Institute of Science, Bangalore, India

P5 Design and Stabilization of Stem Derived Immunogens from HA of Influenza A Viruses

T. Ahmad Najar, R. Varadarajan

Indian Institute of Science, Bangalore, India

P6 Mechanisms of Immunogenicity Provided by Eilat Virus-Based Vaccines

J. Auguste, J. Erasmus

University of Texas Medical Branch, Galveston, TX

P7 Probing the Humoral Immune Response against Respiratory Syncytial Virus to Guide Rational Vaccine Design

J. S. McLellan

Geisel School of Medicine at Dartmouth, Norwich, VT

P8 Analytics for High Throughput (HT) Vaccine Antigen Characterization

P. Ahl, J. Blue, H. Mach, S. McClure, C. Wang

Merck & Co., Inc.

P9 A Phase II Randomized Controlled Trial of an RSV F Nanoparticle Vaccine in Older Adults: Epidemiology and Efficacy

K. Carroll¹, L. Fries¹, G. Glenn¹, S. P. Hickman¹, D. Jani¹, E. P. Kpamegan¹, P. A. Piedra³, V. Shinde³, D. Thomas¹

¹Novavax, Gaithersburg, MD; ²Baylor College of Medicine, Houston, TX
P10 Immunogenicity and Safety of Bivalent rLP2086, a Meningococcal Serogroup B Vaccine, in Adolescents and Young Adults in Two Pivotal Phase III Trials
1Pfizer Vaccine Research, Pearl River, NY; 2Pfizer Ltd, Tadworth, United Kingdom; 3Arhus Universitetshospital, Aarhus, Denmark; 4Pfizer Vaccine Research, Collegeville, PA; 5Senders Pediatrics, South Euclid, OH; 6University of Tampere Medical School, Tampere, Finland; 7Research Institute of the McGill University Health Center, Montreal, Quebec, Canada

P11 Economic Burden of Diagnosed Pertussis among Individuals with Asthma or Chronic Obstructive Pulmonary Disease: A US Database Study
P. O. Buck1, K. L. Davis2, L. Gordon1, S. Kurosky2, J. Meyers2, R. Parikh2
1GlaxoSmithKline, Philadelphia, PA; 2RTI Health Solutions, Research Triangle Park, NC

P12 Mapping Phenotypic Plasticity Across the Life-Course Following Childhood Vaccination
M. Hollm-Delgado, E. Stuart, R. Black
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

P13 Time to Switch to the 9-Valent Human Papillomavirus (HPV) Vaccine in the United States
A. B. Berenson, F. Guo, J. M. Hirth
University of Texas Medical Branch, Galveston, TX

P14 Vaccinations against Smallpox and Tuberculosis Are Associated with Better Long-Term Survival: A Danish Observational Case-Cohort Study 1971-2010
P. Aaby1, J. Baker2, C. Benn1, L. Haugaard3, H. Ravn5, A. Rieckmann4, A. Roth7, S. Sørup6, M. Villumsen8
1Bandim Health Project, Indepth Network, Guinea-Bissau; 2Bispebjerg Hospital, Frederiksberg, Denmark; 3Statens Serum Institut/University of Southern Denmark, Copenhagen, Denmark; 4Institute of Preventive Medicine, Denmark and Novo Nordisk Foundation Center for Basic Metabolic Research, Frederiksberg, Denmark; 5Statens Serum Institut, Copenhagen, Denmark; 6Research Center for Vitamins and Vaccines (CVIVA), Bandim Health Project, Statens Serum Institut, Copenhagen, Denmark; 7Swedish Public Health Authority, Solna, Sweden; 8Health Data and ICT, Copenhagen, Denmark

P15 Who Is the “Herd” in Herd Immunity?: How Herd Definition Affects Vaccination Coverage Rates and Herd Immunity Status
P. L. Delamater, K. H. Jacobsen, T. F. Leslie, E. J. Street, Y. T. Yang
George Mason University, Fairfax, VA

P16 Measles Immunity and Illness in Tianjin, China
M. Boulton1, B. Carlson3, J. Montgomery1, A. L. Wagner3, X. Wang3, Y. Zhang3
1University of Michigan School of Public Health, Ann Arbor, MI; 2University of Michigan, Ann Arbor, MI; 3Tianjin Centers for Disease Control and Prevention, Tianjin, China

P17 Developing Canadian Human Health Vaccine Priorities
E. Rud, J. Spika, R. Thomas-Reilly, L. Williams
Public Health Agency of Canada, Ottawa, Ontario, Canada
P18  Distinct Challenges in Cost-Effectiveness Analysis Modelling of HPV Vaccines in Low and Middle Income Countries: A Systematic Review  
O. Ikechukwu Ekwunife¹, A. Gerber Grote², S. Lhachimi³, C. Mosch⁴, J. O’Mahony⁵, T. Paeck³  
¹Alexander von Humboldt Foundation, Bremen, Germany; ²Institute for Quality and Efficiency in Health Care, Cologne, Germany; ³Bremen University, Bremen, Germany; ⁴Universität Witten, Herdecke, Germany; ⁵Centre for Health Policy and Management, School of Medicine, Trinity College, Dublin, Ireland

P19  An Opsonophagocytic Assay to Evaluate Immunogenicity of Non-Typhoidal Salmonella Vaccines  
G. Ramachandran¹, M. Boyd¹, J. MacSwords¹, E. Higginson¹, R. Simon¹, M. Pasetti², M. Levine¹, S. Tennant¹  
¹University of Maryland, School of Medicine, Baltimore, MD; ²University of Maryland, Baltimore, Baltimore, MD

P20  Antigen Density Is a Critical Determinant of the Humoral Immune Response to Model Viral Antigens Displayed on a Nanoparticle Scaffold  
M. Brewer, S. Dewhurst, C. Feng  
University of Rochester, Rochester, NY

P21  Development of a Common Platform to Assess Neutralizing Antibodies to Pathogenic Human Viruses  
S. Lee, K. Peden, K. Phy, L. Sheng-Fowler, W. Tu  
US Food and Drug Administration, Silver Spring, MD

P22  Highly Cross-Conserved Burkholderia T Cell Epitopes Generate Effector T Cell Responses in Vitro  
M. Ali¹, M. Ardito², A. S. De Groot¹², R. Liu¹, W. Martin², L. Moise³, R. Tassone¹, F. Terry²  
¹Institute for Immunology and Informatics - University of Rhode Island, Providence, RI; ²EpiVax Inc., Providence, RI

P23  Identification of Pathogen Immunoevasion Triggers Using JanusMatrix: Implications for Vaccine Design  
C. Bailey-Kellogg², S. Gregory³, A. H. Gutierrez¹, R. Liu¹, P. Losikoff⁴, R. Tassone¹, F. Terry⁵  
¹Institute for Immunology and Informatics - University of Rhode Island, Providence, RI; ²Dartmouth College, Hanover, NH; ³University of Rhode Island, Providence, RI; ⁴Lifespan, Providence, Rhode Island; ⁵EpiVax. Inc., Providence, RI

P24  Programming Anti-Tumor Immunity through Self-Assembly of Molecular Adjuvants  
Y. Chiu, J. M. Gammon, C. M. Jewell  
University of Maryland - College Park, College Park, MD

P25  RT-qPCR-Based Microneutralization Assay for Human Cytomegalovirus Using Fibroblasts and Epithelial Cells  
H. Murata, X. Wang  
US Food and Drug Administration, Silver Spring, MD

P26  SACOL1789, a Putative Stress Response Protein, Is a Protective Vaccine Antigen in the Model of Soft Tissue and Skin Infection of Staphylococcus aureus  
B. L. Cheng¹, S. Boyle-Vavra¹, K. Bruhn², R. S. Daum³, C. P. Montgomery¹, B. Spellberg²  
¹University of Chicago, Chicago, IL; ²University of Southern California, Los Angeles, CA
P27 Predicting Relatedness of PRRSv Strains Based on Whole Genome T Cell Epitope Content
A. S. De Groot\textsuperscript{1,3}, A. H. Gutierrez\textsuperscript{2}, C. Loving\textsuperscript{3}, W. Martin\textsuperscript{4}, L. Moise\textsuperscript{4}
\textsuperscript{1}Institute for Immunology and Informatics - University of Rhode Island, Providence, RI; \textsuperscript{2}USDA-ARS-National Animal Disease Center, Ames, Iowa; \textsuperscript{3}EpiVax Inc., Providence, RI

P28 Clinical Trial Regulatory Compliance Challenges in Research Naïve Locations
S. Garg, S. Leister
Technical Resources International, Inc., Bethesda, MD

P29 Facilitators and Barriers of HPV Vaccination in a Sample of Urban Young Men Who Have Sex with Men
H. B. Fontenot
Boston College, Newton, MA

P30 Joint Frailty Mixed Models: Accounting for Heterogeneity in Sieve Analysis of Vaccine Efficacy
P. Edlefsen, J. Shao
Fred Hutchinson Cancer Research Center, Seattle, WA

P31 Predicting Influenza in Primary Care Using Classification and Regression Tree Analysis (CART)
G. Balasubramani\textsuperscript{1}, E. Belongia\textsuperscript{2}, L. Clipper\textsuperscript{3}, H. Eng\textsuperscript{4}, B. Flannery\textsuperscript{4}, M. Gaglani\textsuperscript{3}, L. Jackson\textsuperscript{5}, M. Jackson\textsuperscript{5}, R. Malosh\textsuperscript{6}, H. McLean\textsuperscript{7}, A. Monto\textsuperscript{6}, M. Nowalk\textsuperscript{1}, L. Urbanski\textsuperscript{6}, S. Wisniewski\textsuperscript{1}, R. Zimmerman\textsuperscript{1}
\textsuperscript{1}University of Pittsburgh, Pittsburgh, PA; \textsuperscript{2}Marshfield Clinic Research Foundation, Marshfield, WI; \textsuperscript{3}Baylor Scott and White Health, Temple, TX; \textsuperscript{4}Centers for Disease Control and Prevention, Atlanta, GA; \textsuperscript{5}Group Health Research Institute, Seattle, WA; \textsuperscript{6}University of Michigan, Ann Arbor, MI; \textsuperscript{7}University of Pittsburgh Medical Center, Natrona Heights, PA

P32 Determinants of Human Papillomavirus (HPV) Vaccine Uptake among US Military Personnel
J. Buechel
University of San Diego, San Diego, CA

P33 The Association of Health Seeking Behaviors with HPV Vaccination Status among High-Risk Urban Youth
H. B. Fontenot
Boston College, Newton, MA

P34 Gender and Ethnicity Are Important Characteristics for Inclusion and Analysis in Clinical Trials: An Annotated Bibliography
P. E. Kilgore\textsuperscript{1}, Y. Liang\textsuperscript{2}, A. Salim\textsuperscript{3}
\textsuperscript{1}Wayne State University, Detroit, MI; \textsuperscript{2}Institute of Medical Biology, Chinese Academy of Medical Science, Peking Union Medical College, Kunming, China

P35 Characterization of New Live, Attenuated Shigella flexneri Vaccine Candidates
E. M. Barry, B. DeLaine, C. Grassel, T. Wu
University of Maryland School of Medicine, Baltimore, MD
**POSTER SESSIONS**

**P36** Characterization of the Highly Protective Live Attenuated Tularemia Vaccine Candidate, Schu S4ΔaroD
A. L. Cunningham\(^2\), B. J. Mann\(^3\), A. Qin\(^1\), C. Grassel\(^1\), E. M. Barry\(^1\)
\(^1\)University of Maryland School of Medicine, Baltimore, MD; \(^2\)University of Maryland Baltimore, Baltimore, MD; \(^3\)University of Virginia, Charlottesville, VA

**P37** Cutaneous Deficiency of Filaggrin and STAT3 Exacerbates Vaccinia Disease in Vivo: Role of TGFβR Signaling
Y. He, J. Reed, I. Sultana, K. Takeda
US Food and Drug Administration, Center for Biologics Evaluation and Research, Silver Spring, MD

**P38** Development of Animal Model of Progressive Vaccinia (PV) in Nude Mice Using Bioluminescence Imaging: Assessment of Protection by Anti-Vaccinia Monoclonal Antibodies
S. Crotty\(^1\), H. Golding\(^2\), A. Thomas\(^1\), M. Zaitseva\(^2\)
\(^1\)The University of Texas Health Science Center at San Antonio, San Antonio, TX; \(^2\)US Food and Drug Administration, Center for Biologics Evaluation and Research, Silver Spring, MD; \(^3\)US Food and Drug Administration, Silver Spring, MD

**P39** Fusion of Dendritic Cell-Targeting Chemokine MIP3α to Melanoma Antigen Gp100 Significantly Enhances Survival Compared to Antigen-Only Therapeutic DNA Vaccination in Mouse Melanoma Model System
J. Gordy, R. Markham
Johns Hopkins University, Baltimore, MD

**P40** *Streptococcus pyogenes* Vaccination with Peptide Amphiphile Micelles
J. Barrett, M. Tirrell
University of Chicago, Chicago, IL

**P41** Self-Assembled Immune Signals as a Platform for T Cell Vaccination
C. M. Jewell, P. Zhang
University of Maryland, College Park, MD

**P42** Madin Darby Canine Kidney Cell Single-Cell Clones Have an Unstable Non-tumorigenic Phenotype
G. Foseh, A. M. Lewis, Jr., R. Omeir, K. Peden, K. Phy, W. Tu
US Food and Drug Administration, Silver Spring, MD

**P43** Biophysical Characterization of an *E. coli* Expressed CRM197 Conjugate Vaccine Carrier Protein
A. Lees\(^1\), N. Oganesyan\(^1\), M. Ollivault-Shiflett\(^1\), S. Kronheim\(^1\), F. Robb\(^2\), R. Simon\(^2\), J. Van Druff\(^2\)
\(^1\)Fina Biosolutions LLC, Rockville, MD; \(^2\)University of Maryland, Baltimore, MD

**P44** Knowledge, Attitudes, Beliefs, and Behaviors of College Students and Staff during a Meningococcal B Outbreak Vaccination Program: A Canadian Immunization Research Network (CIRN) Study
D. M. MacDougall\(^1\), J. Langley\(^4\), S. McNeil\(^4\), K. A. Top\(^4\), B. Halperin\(^4\), L. Li\(^4\), D. MacKinnon-Cameron\(^4\), A. Swain\(^4\), J. A. Bettinger\(^1\), E. Dube\(^2\), G. De Serres\(^2\), S. Halperin\(^4\)
\(^1\)University of British Columbia, Vancouver, British Columbia, Canada; \(^2\)INSPQ, Quebec City, Quebec, Canada; \(^3\)St. Francis Xavier University, Antigonish, Nova Scotia, Canada; \(^4\)Dalhousie University, Halifax, Nova Scotia, Canada; \(^5\)Acadia University, Wolfville, Nova Scotia, Canada
**P45**  
**Influence of e-Health Text Messages Linked to Health Portal on College Students’ Influenza Vaccine Rate**  
C. Sharbaugh  
Haverford College, Haverford, PA

**P46**  
**Developing a Synthetic DNA Vaccine for an Emerging Pathogen - Middle East Respiratory Syndrome**  
D. Falzarano¹, H. Feldmann², A. Khan³, J. Kim³, G. Kobinger⁴, K. A. Kravnyak⁵, S. B. Kudchodkar⁶, J. Maslow⁶, K. Muthumani⁵, Y. K. Park⁴, **E. Reuschel**⁷, N. Y. Sardesai¹, C. Tingey⁷, D. Weiner⁵  
¹Vaccine and Infectious Disease Organization - International Vaccine Centre, Saskatoon, Saskatchewan, Canada; ²National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, MT; ³Inovio Pharmaceuticals, Plymouth Meeting, PA; ⁴Public Health Agency of Canada, Winnipeg, Manitoba, Canada; ⁵University of Pennsylvania, Philadelphia, PA; ⁶GeneOne Life Sciences, Inc., Villanova, PA

**P47**  
**Effect of Adjuvant Formulation on the Immunogenicity and Protective Efficacy of *Salmonella* Enteritidis Core-OPS (COPS) Conjugates with Flagellin in Infant and Adult Mice**  
S. M. Baliban¹, G. Ramachandran², R. S. Laufer¹, M. Pasetti¹, R. Simon²  
¹University of Maryland, Baltimore, Baltimore, MD; ²University of Maryland, School of Medicine, Baltimore, MD

**P48**  
**The iVAX Toolkit: A Powerful Suite of in Silico Vaccine Design and Analysis Algorithms**  
EpiVax, Inc., Providence, RI

**P49**  
**Immunoinformatic Approaches to Identifying Novel *Ehrlichia chaffeensis* Vaccine Candidates**  
J. W. McBride, T. Velayutham, X. Zhang  
University of Texas Medical Branch, Galveston, TX

**P50**  
**A Recombinant Subunit Vaccine for Bovine RSV and *Histophilus somni* Protects Calves against Dual Pathogen Challenge**  
L. J. Gershwin³, L. B. Corbeil¹  
¹University of California, San Diego, San Diego, CA; ³University of California, Davis, Davis, CA

**P51**  
**DNA Vaccination Encoding Beta Toxin of *Clostridium perfringens* Combined with Heterologous Booster Elicits Protective Immune Response in Mice**  
A. Solanki, B. Bhatia, L. Garg  
National Institute of Immunology, New Delhi, India

**P52**  
**Detection of Hepatitis B Virus Immune Escape Mutants Among Asymptomatic Population Group in Southwestern Nigeria**  
O. M. Adewumi¹, A. Bakarey¹, T. O. Faleyè², I. Maryjoy Ifeora¹  
¹University of Ibadan, Ibadan, Nigeria; ²Ekiti State University, Ado Ekiti, Nigeria
P53  Preparing for an Outbreak of Ebola Virus Disease in Nigeria: Barriers and Safety Concerns of the Use of the Ring Vaccination Design
O. Onigbogi¹, O. Ojo²
¹IBPH/University of Lagos, Lagos, Nigeria; ²IBPH, Lagos, Nigeria
INVITED SPEAKER BIOGRAPHIES
Niranjan Bhat, MD, MHS
Dr. Bhat received a BA in biochemical sciences from Harvard University, and his MD from Vanderbilt University. Following a residency in pediatrics at Seattle Children’s Hospital/University of Washington in Seattle, he joined the Centers for Disease Control and Prevention as an Epidemic Intelligence Service Officer in the Influenza Branch, and continued on as a medical epidemiologist with this group. He then trained in Pediatric Infectious Diseases at Johns Hopkins University (JHU), after which he joined the faculty in the Department of Pediatrics and obtained a Masters in Health Sciences in Clinical Investigation. He subsequently moved from JHU to serve for two years as a clinical reviewer in the US Food and Drug Administration Office of Vaccines, before joining the Vaccine Access and Delivery Program as a Senior Clinical Officer at PATH, in Seattle. Dr. Bhat has spent the majority of his career researching respiratory infections and vaccines in children, while in recent years his work has included research and policy around immunization of pregnant women.

Dennis Burton, PhD
Dr. Burton is the Chairman, and professor in the Department of Immunology and Microbial Science, The Scripps Research Institute, La Jolla. He was recently awarded the James and Jessie Minor Chair in Immunology. He received his BA in Chemistry from Oxford University and his PhD from Lund University, Sweden in physical biochemistry. He is the Scientific Director of the International AIDS Vaccine Initiative (IAVI) Neutralizing Antibody Consortium and Neutralizing Antibody Center, Director of The Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery (CHAVI-ID) at Scripps, and a member of the Ragon Institute of MGH, MIT, and Harvard. He has held many research grants from the National Institutes of Health (NIH) and has published more than 350 papers in scientific journals. He has received numerous awards including the Jenner Fellowship of the Lister Institute and a Fellowship in the American Academy of Microbiology. His research is focused on infectious disease, in particular the interplay of antibodies and highly mutable viruses, notably HIV. He is interested in the potential of broadly neutralizing antibodies to inform vaccine design.

Marina Caskey, MD
Dr. Marina Caskey graduated from medical school at the Federal University of Sergipe in Brazil, and trained in infectious diseases at Weill Cornell Medical Center in New York. She is an assistant professor of Clinical Investigation at the Rockefeller University. Her scientific work focuses on the clinical evaluation and development of novel immunotherapeutic strategies against infectious diseases, with a special emphasis on HIV-1. She is conducting a series of phase 1 studies in HIV-infected and HIV-uninfected individuals to evaluate the safety and activity of anti-HIV broadly neutralizing antibodies. These antibodies are promising new immunotherapeutic investigational products, being developed for potential roles in HIV-1 prevention and therapy.

Robert S. Daum, MD, CM
Dr. Daum is a nationally and internationally known expert in Pediatric Infectious Diseases and currently heads the University of Chicago Medical Center MRSA Research Center.

In 1998, Dr. Daum published a paper documenting that methicillin-resistant Staphylococcus aureus (MRSA) had become a major problem in the community. Previously, MRSA had been known to be a problem only in healthcare facilities. A decade later, this concept of a community-based epicenter of MRSA infections has changed the research focus necessary to understand this new problem. Indeed, epidemic MRSA disease in the community has now been declared a public health imperative.

Previously, Dr. Daum has played a vital role in understanding the immune response to Haemophilus Influenzae type b vaccines and was one of the key investigators involved in understanding the immune response of children to these vaccines.

Dr. Daum is also the director of the Pediatric Immunization Program (PIP), a "reminder-recall on foot" program in Chicago aimed at developing a
novel strategy for delivering routine immunizations to children.

Dr. Daum graduated from McGill University, Montreal, completed residency and research training at Montreal Children's, and completed his Infectious Diseases Fellowship at Children's Hospital, Harvard Medical School. In 1978, he was appointed to the faculty at Tulane University. In 1988, he moved to the University of Chicago where he has remained.

Aravinda de Silva, PhD

Dr. de Silva graduated from Vassar College in 1986 with a major in Biology. He then joined the PhD program in the Department of Cell Biology at the Yale University School of Medicine. At Yale he did his doctoral work with Ari Helenius on the folding, assembly, and sorting of viral membrane proteins. After doing postdoctoral work at the University of Rochester and Yale University, Dr. de Silva joined the Department of Microbiology and Immunology at the University of North Carolina at Chapel Hill in 1998. He is interested in vector-borne infectious diseases and mainly studied how ticks transmit Lyme disease spirochetes for the first part of his career. Currently his group works on dengue virus. Dr. de Silva is interested in many aspects of dengue including population-based epidemiological studies, viral pathogenesis, human immunology, and vaccine research. He also has a great interest in working with scientists and students from developing countries to promote a culture of science and scientific independence in all countries.

Elisabeth Erlacher-Vindel, PhD

Dr. Erlacher-Vindel graduated from the Veterinary University, Vienna, Austria. She was first employed and obtained her doctoral degree in the Institute of Breeding and Genetics (Vienna, Austria) and later worked in Paris in the Institut Pasteur.

After having worked as a field veterinarian in different countries, she worked in a professional dairy organisation, where she became the Deputy Director of the Scientific Department and Head of the Food Safety and Environment Unit. She dealt with research and provided advice and expertise in the field of animal health, food safety, veterinary drugs and environmental issues.

Her current position since September 2008 is Deputy Head of the Scientific and Technical Department of the World Organisation for Animal Health (OIE) where she is in particular in charge of the dossiers related to veterinary products, including antibiotics.

Cara Fiore, PhD

Dr. Fiore is a master reviewer with the Center for Biologics Evaluation and Research within the US Food and Drug Administration. Previously, she was a senior scientist with Office of Biomedical Advanced Research and Development Authority within the Department of Health and Human Services. She earned her BS in Biology from Tulane University in New Orleans, LA and her PhD from the University of Maryland School of Medicine in Baltimore, MD.

Richard L. Gorman, MD

Dr. Gorman earned his BA in Physics at the Catholic University of America and his MD from the State University of New York, Downstate. He completed a Robert Wood Johnson General Pediatric Academic Development Fellowship at Johns Hopkins Hospital.

Dr. Gorman has been the director of the University of Maryland Pediatric Emergency Department, Medical Director of the Maryland Poison Center, and Chair of the AAP Committee on Drugs. He practiced pediatric primary care in suburban Maryland for 20 years. Since 2008, Dr. Gorman has served as the associate director for Clinical Research at the Division of Microbiology and Infectious Disease at the National Institute for Allergy and Infectious Disease at NIH. In this role, he directs clinical research on vaccines, therapeutics, and diagnostics to advance the protection, diagnosis, and treatment of individuals susceptible to infectious diseases.

Dr. Gorman’s professional goal has always been to improve the health of children. He has pursued these goals through direct provision of care, supervising or administering care delivered to children, developing policies and legislation to improve children’s care and guiding research into expanding the knowledge base.
BARNEY S. GRAHAM, MD, PhD
Dr. Graham is an immunologist, virologist, and clinical trials physician whose primary interests are viral pathogenesis, immunity, and vaccine development. His work is focused on HIV, respiratory syncytial virus (RSV), and emerging viral diseases. After graduating from Rice University, he obtained his MD from the University of Kansas School of Medicine in 1979. He then completed residency and two chief residencies in Internal Medicine, a fellowship in Infectious Diseases, and a PhD in Microbiology & Immunology at Vanderbilt University School of Medicine, where he rose to the rank of professor of medicine with a joint appointment in the Department of Microbiology & Immunology. In 2000, he became one of the founding investigators for the NIAID Vaccine Research Center at NIH where he is now the Deputy Director and Chief of the Viral Pathogenesis Laboratory. He is known for his broad knowledge of viral pathogenesis, immunology, and vaccine development, and contributions to both basic and clinical research. He is a member of the American Society for Clinical Investigation and the American Association of Physicians, a Fellow of the Infectious Disease Society of America and the American Academy of Microbiology, and a recipient of the Robert M. Chanock Award for lifetime contributions to RSV research. He serves on several editorial boards, and as a consultant for WHO and other organizations involved in vaccine development for HIV, RSV, Tb, malaria, and Ebola.

MARRION F. GRUBER, PhD
Dr. Gruber is the director of the Office of Vaccines Research and Review (OVRR) in the Center for Biologics Evaluation and Research (CBER), US Food and Drug Administration. In this position, she directs the review, monitoring, and evaluation of investigational new drug applications and biologic license applications encompassing vaccines and related biological products as well as research pertaining to the development, manufacturing and testing of vaccines. From 2009-11 Dr. Gruber served as OVRR Deputy Director and from 2005-09 as OVRR Associate Director for Policy. In these positions she has gained extensive experience in developing policies and programs affecting the regulation of vaccines. Dr. Gruber has served on numerous agency and interagency working groups and committees and has represented the OVRR on national and international task forces to foster communications and collaborations related to the safety, quality and efficacy of vaccines. Dr. Gruber has over 20 years of experience in the regulatory review and approval of preventive vaccines and related biologics. She has generated guidance for industry documents critical to the development of preventive vaccines and has contributed to rule making affecting the regulation of vaccines. She has represented OVRR in numerous FDA wide initiatives, as well as national and international meetings.

COL PAUL B. KEISER, MD
Dr. Keiser is director of the Viral Diseases Branch at the Walter Reed Army Institute of Research and a practicing allergist at the Walter Reed National Military Medical Center. He has deployed twice to Afghanistan with aviation and infantry task forces and is an honor graduate of the Fort Lee Command and General Staff Officer’s Course.

COL Keiser received his MD from Washington University in Saint Louis. He completed his residency in Internal Medicine at Georgetown and fellowships in Infectious Disease at the NIH Clinical Center and in Allergy/Immunology at Walter Reed. He has authored or co-authored more than 25 scientific papers and book chapters.

BRUCE Y. LEE, MD, MBA
Dr. Lee is associate professor of International Health at the Johns Hopkins Bloomberg School of Public Health, director of the Global Obesity Prevention Center (GOPC) at Johns Hopkins and director of...
Operations Research at the International Vaccine Access Center (IVAC). Dr. Lee has over 15 years of experience in industry and academia in public health operations research and systems science, which involves developing and utilizing mathematical and computational methods, models, and tools to help stakeholders better understand decision making, processes, and systems. He has been the Principal Investigator for a number of projects supported by a variety of organizations and agencies including the Bill and Melinda Gates Foundation, the National Institutes of Health (NIH), the Agency for Healthcare Quality and Research (AHRQ), the Centers for Disease Control and Prevention, UNICEF, Global Good, and the Global Fund. He and his work have garnered attention in leading media outlets such as the New York Times, Los Angeles Times, Businessweek, US News and World Report, Bloomberg News, Nature Medicine, and National Public Radio (NPR). Dr. Lee received his BA from Harvard University, MD from Harvard Medical School, and MBA from the Stanford Graduate School of Business. He completed his internal medicine residency training at the University of California, San Diego.

Mario A. Monteiro, PhD
Dr. Monteiro is a professor in the Department of Chemistry at the University of Guelph. He attained his PhD at York University under the supervision of Professor Gerald Aspinall in 1996. Following his doctorate, Dr. Monteiro joined the research group of Dr. Malcolm Perry at the National Research Council Canada with funding from the Canadian Bacterial Diseases Network. In 2001, he moved to the US to work at Wyeth (now Pfizer Inc.) as a Senior Scientist in the Carbohydrate division. Dr. Monteiro returned to Canada in 2004 to take up a faculty position in the Department of Chemistry at the University of Guelph. His current research interests include the discovery of carbohydrate-based vaccines against human gastric-pathogens. Most notably so far, he has created and licensed two key vaccines: one against traveller’s diarrhea (anti-Campylobacter jejuni) that is now in phase 1 human trials in the US; and another against Clostridium difficile that is now in pre-clinical trials at a US-based biotech company. In 2014, he was listed in the Top 50 list of the most influential people in vaccines. His new campaign focuses on the development of vaccines to combat gastric infections associated with diarrhea in autistic children.

M. Anthony Moody, MD
Dr. Moody received his MD from Duke School of Medicine, was a resident and chief resident at Emory Pediatrics, and then a fellow in Pediatric Infectious Diseases at Duke. He is currently associate professor of Pediatrics at Duke and the Chief Medical Officer for the Duke Human Vaccine Institute. He directs the Laboratory of B Cell Immunotechnology that develops tools to study B cell responses to vaccines and infection, including HIV-1. Using these techniques, Dr. Moody’s laboratory quantitates and isolates antigen-specific B cells by polychromatic flow cytometry, and the phenotypic panels give detailed characterization of B cells to correlate changes in B cell populations with other components of the immune system. Dr. Moody is part of a large, multi-disciplinary team that has used antigen specific B cell and plasmablast/plasma cell sorting to isolate immunoglobulin genes using PCR. This team has produced >10,000 human and >4,000 rhesus monoclonal antibodies. Analyses of antibody clonal lineages, including monoclonal antibodies derived from HIV-1-infected participants, have demonstrated the co-evolution of the envelope glycoprotein of HIV-1 during infection and infection-elicited antibodies. The pathways defined by this co-evolutionary process are being harnessed to develop new AIDS vaccine candidates.

Vasee Moorthy, PhD
Dr. Moorthy is an infectious diseases physician, immunologist, and product developer, with previous experience working as a clinical lecturer at the University of Oxford, for PATH in the US, and as a general medical officer at Hlabisa Hospital, Kwazulu-Natal, South Africa. His current position at WHO is as both Team Lead for the MERS-CoV element of the blueprint workstream 2, and also as Team Leader for Vaccine Development, in the Department of Immunization, Vaccines, and Biologicals. He acted
as Phase 1-2 Vaccines Team Lead in the Ebola R&D Team during the 2014-2015 Emergency, coordinating many clinical trials in North America, Europe, and Africa. Dr Moorthy qualified as a physician with an undergraduate degree from the University of Cambridge and a clinical medicine degree from the University of Oxford. He has a PhD in immunology gained during three years based at MRC Laboratories in The Gambia.

Flor Munoz-Rivas, MD
Dr. Munoz-Rivas is associate professor of Pediatrics and Molecular Virology and Microbiology at Baylor College of Medicine. She is a pediatric infectious diseases specialist interested in the epidemiology and prevention of infections in young infants with vaccines and maternal immunization. She has over 18 years of experience in clinical research, being responsible for the design and implementation of phase I to IV pediatric and maternal immunization studies, and studies of antivirals in children. Dr. Munoz is ID Consultant and Medical Director of Transplant Infectious Diseases at Texas Children’s Hospital, and IRB Chair at Baylor College of Medicine.

Saad B. Omer, MBBS, MPH, PhD
Dr. Omer is a professor of Global Health, Epidemiology, and Pediatrics at Emory University, Schools of Public Health and Medicine. He is also a faculty member at the Emory Vaccine Center. He has conducted multiple studies – including vaccine trials – in Guatemala, Uganda, Ethiopia, India, Pakistan, Bangladesh, South Africa, and the United States. Dr. Omer’s research portfolio includes clinical and field trials to estimate efficacy and/or immunogenicity of influenza, polio, measles, and pneumococcal vaccines; studies on the impact of spatial clustering of vaccine refusers; and clinical trials to evaluate drug regimens to reduce mother-to-child transmission of HIV in Africa. He has conducted several studies to evaluate the roles of schools, parents, healthcare professionals, and state-level legislation in relation to immunization coverage and disease incidence. Dr. Omer has published widely in peer reviewed journals including the New England Journal of Medicine, JAMA, the Lancet, British Medical Journal, Pediatrics, American Journal of Public Health, and American Journal of Epidemiology.

Peter Palese, PhD
Dr. Palese is professor of Microbiology and Chair of the Department of Microbiology at the Icahn School of Medicine at Mount Sinai, New York. 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 and function relationships of viral genes, for investigation of viral pathogenicity, and for development and manufacturing of novel vaccines. In addition, an improvement of the 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 García-Sastre has revealed that most negative strand RNA viruses possess proteins with interferon antagonist activity, enabling them to counteract the antiviral response of the infected host. 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, a recipient of the European Virology Award (EVA) in 2010, a recipient of the 2012 Sanofi-Institut Pasteur Award and received the 2015 Beijerinck Virology Prize from the Royal Netherlands Academy of Arts and Sciences. He is a Member of the National Academy of Sciences (2000), a Member of the Institute of Medicine (2012) and he has been elected a Fellow of the American Academy of Arts and Sciences (2014).
Caroline M. Poland, MA, LMHC, LCAC, NCC

Ms. Poland is a licensed mental health and clinical addictions counselor, and is the assistant director of the Counseling Center at Taylor University in Upland, IN. She received her undergraduate degree from Taylor University, and received her master’s degree in Clinical Mental Health Counseling at Indiana Wesleyan University, where she was the first in her program to design and pursue an original research track resulting in a written thesis, titled “The Effectiveness of a Wellness Group Intervention for College Students.” Her areas of interest include work-life balance, wellness, anxiety, depression, addictions, and health decision making. Ms. Poland has recently authored several papers exploring the effect of cognitive bias on vaccine acceptance decision-making, and has developed a model called “Preferred Cognitive Styles and Health Decision Making.” Ms. Poland has been a guest lecturer at both Taylor University and Indiana Wesleyan University, as well as at the US Air Force Academy, the Universidad Del Azuay in Cuenca, Ecuador, Hospital Del Rio in Cuenca, Ecuador, the Mayo Clinic International Medical Education Conference in Athens, Greece, University of Athens Children’s Hospital, Azusa Pacific University, Duke University, Minnesota Medical Association, the Iowa Immunization Conference, and an international influenza meeting in Valencia, Spain. She recently participated as a faculty member in an Expert Forum on behavioral health and vaccine acceptance, as well as a meeting on public trust in vaccines.

Gregory A. Poland, MD

Dr. Poland is the director of Mayo Clinic’s Vaccine Research Group – a state-of-the-art research group and laboratory that seeks to understand the genetic drivers of viral vaccine response and investigates issues surrounding novel vaccines important to public health. The Poland lab has developed the field of viral vaccine immunogenetics, the immune response network theory, and the fields of vaccinomics and adversomics.

Dr. Poland holds the academic rank of professor of medicine and infectious diseases and molecular pharmacology and experimental therapeutics. He is the founding president of the Edward Jenner Vaccine Society and is Editor in Chief for the journal Vaccine.

Dr. Poland is also the 2013 recipient of the Mayo Distinguished Investigator award by the Mayo Board of Trustees, and the 2012 recipient of the Mayo Clinic Department of Medicine Lifetime Research Achievement Award. In 2012, Dr. Poland was named in the top 25 vaccine influencers in the world. In February 2013, he was nominated for membership in the Institute of Medicine (IOM). In addition, he received an NIH MERIT Award, an honor accorded to less than 5% of the nation’s NIH-funded investigators. Dr. Poland was awarded the Secretary of Defense Award for Excellence in December 2008. In 2008, he was named a Master of the American College of Physicians. Dr. Poland received the Hsu prize in International Infectious Disease Epidemiology in 2007, and the Charles Mérieux Lifetime Achievement Award in Vaccinology from the National Foundation for Infectious Diseases in May 2006. In December 2006, Dr. Poland was elected President of the Defense Health Board, serving two terms. In 2005 he was awarded an honorary Doctor of Humane Letters by Illinois Wesleyan University, his alma mater. He was appointed as the Mary Lowell Leary Professor in Medicine (the highest academic distinction for a faculty member) by Mayo Clinic’s Board of Trustees in 2004. In May 2003, he was awarded the Secretary of Defense Medal for Outstanding Public Service for his leadership in writing the Department of Defense’s bioterrorism countermeasures. Since 2004, Dr. Poland has served on the Infectious Diseases Society of America (IDSA) Taskforce on Pandemic Influenza, and chaired the American College of Physician’s Adult Immunization Advisory Board. Dr. Poland received the inaugural Gold Medal from the Spanish Vaccinology Society in 2001. He is the immediate past president of the Department of Defense’s Defense Health Board and the Armed Forces Epidemiological Board.

Dr. Poland participates on many national and academic review committees has published over 485 peer-reviewed scientific articles and book chapters.
He has received over $180 million in federal funding for his research thus far in his career.

Dr. Poland received his medical degree from the Southern Illinois University School of Medicine in Springfield, IL., and completed his residency and advanced post-graduate work at the University of Minnesota/Abbott-Northwestern Hospital, Minneapolis, MN.

Bali Pulendran, PhD
Dr. Pulendran is a professor in the Department of Pathology and Laboratory Medicine of the Emory University School of Medicine. He received his PhD in immunology from the Walter & Eliza Hall Institute of the University of Melbourne, Victoria, Australia, and did his post-doctoral training at Immunex Corporation in Seattle, WA.

John-Arne Røttingen, MD, PhD
John-Arne Røttingen is executive director of Infection Control and Environmental Health and at the Norwegian Institute of Public Health; professor of Health Policy at the Department of Health Management and Health Economics, Institute of Health and Society, University of Oslo; and adjunct professor at the Department of Global Health and Population, Harvard School of Public Health. He is associate fellow at the Centre on Global Health Security, Chatham House; Chair of the Board of the Alliance for Health Policy and Systems Research; member of the Scientific Oversight Group of the Institute for Health Metrics and Evaluation, University of Washington, Seattle; member of the International Advisory Committee for the Global Burden of Disease study; and member of the WHO Euro Advisory Committee on Health Research. He has been Director General of the Norwegian Knowledge Centre for the Health Services; Oxford Scholar at Wadham College; Fulbright Fellow at Harvard Kennedy School; and Chair of the Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG), WHO. He received his MD and PhD from the University of Oslo, an MSc from Oxford University, and an MPA from Harvard University.

RADM Anne Schuchat, MD
Dr. Schuchat has been Principal Deputy Director for Centers for Disease Control and Prevention (CDC) and ATSDR since September 2015. She began her public health career in 1988 when she came to CDC as an Epidemic Intelligence Service Officer. She was director of CDC’s National Center for Immunization and Respiratory Diseases from 2006-2015. Other CDC leadership posts include: acting director of the National Center for Infectious Diseases (NCID) and the Center for Global Health; chief of the Respiratory Diseases Branch and Chief Health Officer for CDC’s 2009 H1N1 pandemic influenza response. Dr. Schuchat was the initial medical director of ABCs - the Active Bacterial Core surveillance of the Emerging Infections Program Network and spearheaded prevention of newborn infection from group B streptococcal disease in the 1990s. She also served as CDC’s interim deputy director for Science and Program in early 2009. She was promoted to Rear Admiral in the United States Public Health Service in 2006 and earned a second star in 2010. Dr. Schuchat was elected to the Institute of Medicine of the National Academy of Sciences in 2008.

Globally, Dr. Schuchat has worked in West Africa on meningitis, pneumonia, and Ebola vaccine trials; in South Africa on surveillance and prevention projects, and in China on Beijing’s SARS emergency response. She has authored or co-authored more than 230 scientific articles, book chapters, and reviews. Her contributions have been recognized by receipt of the USPHS Meritorious Service Medal, the American Public Health Association’s Maternal and Child Health Young Investigator Award, the USPHS Physician Research Officer of the Year, and an Honorary Doctorate in Science from Swarthmore College. Dr. Schuchat graduated with highest honors from Swarthmore College and with honors from Dartmouth Medical School and completed her residency and Chief residency in Internal Medicine at NYU’s Manhattan VA Hospital.
David E. Swayne, DVM, PhD

Dr. Swayne received his BS in pre-veterinary medicine from University of Arkansas in 1976, his DVM and MS in Veterinary Pathology from the University of Missouri in 1984, and his PhD in Veterinary Pathology from the University of Georgia in 1987. He is board-certified as a veterinary medical specialist in Veterinary Pathology (1988) and as a Poultry Veterinarian (1992). From 1987-1994, he was a faculty member in the College of Veterinary Medicine, The Ohio State University. Since 1994, he has been the Laboratory Director of US Department of Agriculture’s in house high biocontainment laboratory for poultry health research, the Southeast Poultry Research Center, which is part of the US National Poultry Research Center.

For the past 28 years, his personal research has focused on pathobiology and control of avian influenza in poultry, especially the use of vaccines and vaccination in national and global control efforts. Dr. Swayne has served on World Organization for Animal Health (OIE) committees to update the Avian Influenza chapters in Terrestrial Animal Health Code and Manual, and completed a 16 month sabbatical to study highly pathogenic avian influenza control programs at OIE in Paris. He currently serves as Chair of the Executive Committee for OFFLU, the joint OIE/Food and Agriculture Organization Animal Influenza Network. He has participated in missions or conferences on avian influenza control and biosafety/biosecurity in 44 countries during the past 15 years. He has published over 277 peer-reviewed papers on poultry health issues, primarily in avian influenza. He is the editor of three international reference texts – Diseases of Poultry, Avian Influenza and Animal Influenza – and an associate editor for the journal - Influenza and Other Respiratory Diseases.
INVITED PRESENTATION ABSTRACTS
Towards a Universal Influenza Virus Vaccine
Peter Palese, PhD
Icahn School of Medicine at Mount Sinai
New York, NY

Objectives: List the currently used influenza virus vaccine platforms. Describe the need for annual revaccinations against influenza and not measles. Discuss how to design a long-lasting cross-protective universal influenza virus vaccine.

Abstract: Current influenza virus vaccines - administered annually - predominantly elicit a protective immune response to the immunodominant but variable head of the hemagglutinin. This approach is effective, especially when the vaccine strains closely match the circulating viruses. A novel vaccine strategy involves redirecting the response to the more conserved stalk domain of the hemagglutinin and the immunosubdominant neuraminidase. This can be achieved by using vaccine strains which express chimeric hemagglutinin proteins whereby the head of the hemagglutinin represents an exotic subtype never encountered by humans under natural conditions. Such influenza virus constructs are likely to boost memory B cells directed against conserved domains of the hemagglutinin stalk and of the neuraminidase, and thus should afford broad spectrum protection against a variety of antigenic drift and shift strains.

References:

The Spectrum of Vaccine Resistance: Why Are They Hesitant?
Gregory A. Poland, MD
Edward Jenner Society
Mayo Clinic and Foundation
Rochester, MN

Objectives: Describe the spectrum of vaccine decision-making. Articulate the most common anti-vaccine arguments put forward to justify vaccine rejection, and provide data-driven answers to these objections. Explain the consequences of vaccine rejection.

Abstract: Vaccine acceptance, hesitancy, resistance, and rejection are terms that describe the continuum of vaccine decision-making. In this presentation I will review the nosology of vaccine decision-making, and review the common anti-vaccine arguments put forward to justify vaccine rejection. The consequences of vaccine rejection will also be discussed and a way forward from the point of view of the public health discussed.

Reference:
Caroline M. Poland, MA, LMHC, LCAC, NCC
Taylor University
Upland, IN

Objectives: Describe the patient-centric elements of vaccine decision-making. Articulate the common cognitive styles and biases patients employ in making decisions about vaccines. Use the Preferred Cognitive Styles Model to assist patients in making decisions about vaccine acceptance.

Abstract: Vaccine acceptance and refusal is a complex decision informed by an individual’s cognitive style and biases. Healthcare providers have rarely been taught the psychology behind how patients make health decisions such as vaccine acceptance or rejection. In this presentation, I will review the common cognitive biases and cognitive styles that patients utilize in making such decisions. Additionally, I will present a model useful to healthcare providers in educating patients about vaccine decision-making and improving patient capacity to make healthy choices and decisions.

References:

Vaccine Economics and Utilization
Bruce Y. Lee, MD, MBA
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD

Objectives: Explain what is meant by a systems approach to vaccine decision-making. Review the use of computational modeling to better understand vaccine systems.

Abstract: Vaccine development, distribution, administration, and impact occur within a variety of complex systems. Therefore, single changes can have a range of direct and indirect reverberating effects. Therefore, vaccine decision making requires an understanding of these systems. Computational modeling can better characterize these systems and serve as “virtual laboratories” to test different policies and interventions.

References:
Getting Your Vaccine to Market: A Regulatory Perspective
Cara Fiore, PhD
Center for Biologics Evaluation and Research
US Food and Drug Administration
Bethesda, MD

Objective: Describe the IND vaccine development regulatory process.
Abstract: The US Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Vaccines Research and Review (OVRR) regulates preventive and therapeutic vaccines for infectious disease indications. This presentation will discuss the IND vaccine development regulatory process; including regulatory milestones, use of expanded access INDS for emergency use, and the four Expedited Programs for serious conditions.

References:
1. Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (draft)
2. Guidance for Industry: Expanded Access to Investigational Drugs for Treatment Use — Qs & As (draft)
3. Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics

Who Needs an Ebola Vaccine: Epidemiology and Target Populations Revisited
RADM Anne Schuchat, MD
Centers for Disease Control and Prevention
Atlanta, GA

Objectives: Define groups at high risk for Ebola Virus Disease or serious complications. Review epidemiologic features of the West Africa Ebola outbreak.
Abstract: The speaker will provide background on the key epidemiology features of the West African Ebola outbreak in 2014-16. She will also describe research and findings related to groups at high risk for Ebola Virus Disease and serious complications. Transmission of the virus through various routes leads to greater risk in the selected populations including household and close contacts of infected patients, healthcare workers, and persons involved in traditional burial services.

Reference:

Rapid Assembly of Consortia for Expeditious Testing of Ebola Vaccines
Vasee Moorthy, PhD
World Health Organization (WHO)
Geneva, Switzerland

Objective: Communicate the activities led by WHO to coordinate multiple consortia in expedited clinical evaluation of the two candidate Ebola vaccines that were most advanced as of August 2014.
Abstract: In August 2014, after the current outbreak of Ebola virus disease was declared a public health emergency of international concern by the World Health Organization (WHO), two candidate Ebola vaccines met WHO’s criteria for prioritization, namely robust efficacy in a well-developed non-human primate model, and availability of GMP grade material for clinical testing. The Canadian government donated 800 vials of the replication-competent recombinant vesicular stomatitis virus (rVSV)—vectored Zaire ebolavirus (rVSV-ZEBOV) candidate vaccine to the WHO. The VSV Ebola Consortium (VEBCON) was created under the auspices of the WHO to initiate Phase I studies to facilitate rapid progression to Phase II and III trials in affected countries. In the case of the other candidate vaccine, ChAd3-ZEBOV, the consortia also included sites in North America, Europe and Africa.
For both rVSV-ZEBOV and ChAd3-ZEBOV, WHO worked with all of the following constituencies to facilitate expedited high quality assessments and clinical evaluation: Funding agencies, Regulators, Ethics committees, Manufacturers, Independent oversight including GCP monitoring, and DSMB, Data Management and networks of Principal Investigators and Laboratory Capacity.

During the presentation, the approach to expedited clinical development and testing will be elaborated, so that the audience will gain an overview of the ways the fastest ever timelines were achieved from first vaccination with novel candidates to interim efficacy results from a Phase III efficacy trial.1,4

As additional candidate vaccines reached the clinic, WHO expanded its facilitator role to include these programmes. One core role was to enable expedited information sharing, and the presentation will also include some lessons learned on data and results sharing during Public Health Emergencies.9

References:

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Efficacy Trials in West Africa
John-Arne Røttingen, MD, PhD
Norwegian Institute of Public Health
Oslo, Norway

Objective: Review the efficacy trials performed and planned with three Ebola vaccine candidates in West Africa during the 2014-15 Ebola Viral Disease (EVD) outbreak.

Abstract: The 2014-15 Ebola outbreak in West Africa has by far been the largest and most devastating Ebola outbreak so far with over 28,000 cases and a case fatality rate as high as 90 % in some areas.

Ebola vaccine research has been going on since 1980 with a majority of research funded and conducted by the US military. However, at the start of the epidemic only one vaccine had been tested in clinical trials. Since the correlate of protection for EVD is unknown, a potential vaccine had to be tested during an ongoing
epidemic. Due to the exponential rise in Ebola cases during early autumn of 2014, it was assumed that an effective vaccine could contribute to controlling the epidemic. The WHO facilitated international coordination among all relevant stakeholders, including academic institutions, pharmaceutical industry, policy makers and biodefence research organizations. There was unanimous agreement to fast-track the clinical development of several Ebola vaccine candidates, with two live viral vector vaccines with an Ebola glycoprotein insert as frontrunners (Chimpanzee adenovirus and Vesicular Stomatitis Virus vectors). Both of these had demonstrated 100% protection in non-human primate challenge models and were available as clinical-grade (GMP) vaccine product.

To expedite clinical evaluation of vaccine candidates, parallel and sequential testing in phase I, II and III trials was critical. Phase 1 trials were initiated in US, Europe and Africa for the two leading candidates in September – December 2014, with one candidate releasing phase 1 data in November 2014. Results from these trials proved both candidates to be safe and immunogenic in humans.\(^1\)\(^-\)\(^3\) Initially, three phase III trials were initiated in Liberia, Sierra Leone and Guinea in the midst of the Ebola outbreak.

A Liberian-US consortium led by the NIH implemented a classical 3-armed individually randomized controlled trial (iRCT) in Liberia, with a planned sample size of 28 000 split into the two vaccine candidates in addition to saline as placebo control group (PREVAIL I).\(^4\)

In Sierra Leone, a Sierra Leone-US partnership led by the CDC initiated a stepped wedge RCT (STRIVE), in the form of an unblinded phased randomized vaccine introduction in the target population with 18-24 weeks deferred vaccination between each cluster. Planned sample size was 8,000.

Due to a rapid decline in number of cases it was not possible to conclude these trials with regard to efficacy testing.

In Guinea, authorities and NGOs requested early access to vaccine in risk populations. Inspired by the smallpox eradication program in the 1970’s, an efficacy trial based on a novel ring vaccination study design was adopted\(^6\) (Ebola ca suffit trial). When a new Ebola case was diagnosed, all contacts of the individual were identified forming a so called ring. Half of the rings were randomized to immediate vaccination and the other half to delayed vaccination after 21 days. The incidence of EVD between the two groups was compared after an expected ramp-up period of 10 days. The cluster randomized (cRCT) ring vaccination design ensured a high attack rate at the level of the ring, reducing the sample size and time for results. The choice of vaccine (a recombinant Vesicular Stomatitis Virus vector, rVSV vector) was made using a rational framework assessing the latest data from phase I trials. Interim results published 4 months after study initiation showed a vaccine efficacy of 75-100 %.\(^6\) As a consequence, randomization was stopped and all further clusters of contacts of new EVD cases were offered vaccine. Ultimately, the Ministries of Health in both Sierra Leone and Liberia requested the implementation of ring vaccination around newly defined EVD cases in autumn 2015. Due to its novelty, the study design as expected raised interpretations issues.

The efficacy-studies in all three West African countries have included an embedded sub-study focusing on safety and immunogenicity assessment (n=1500 in Liberia, n=400 in Sierra Leone and n=1200 in Guinea) providing essential data for potential regulatory approval of the vaccines.

The experiences encountered during the Ebola vaccine clinical development point to the need for strong international coordination and cross-cutting collaborations. The international actors in R&D collectively managed to demonstrate efficacy of one vaccine candidate, and progressing several other candidates well into phase II trials in endemic countries. The extent and speed of the vaccine R&D was unprecedented, and may serve as an example for developing vaccines against other emerging infectious diseases.
Ebola Vaccine: Gavi Perspectives
Jon Pearman, MSc
Gavi
Geneva, Switzerland

Objective: Explain Gavi’s role in the recent Ebola outbreak as well as its role in potential infectious disease outbreaks going forward.

Abstract: In the wake of recent Ebola (and more recently Zika) outbreaks, the global community is intensifying efforts to define how it can collectively better prepare for, respond to, and ideally prevent future pandemics. Gavi is already engaged, to a limited extent, in this area through its investments in vaccines for several outbreak diseases, health systems and immunization strengthening support, and recent involvement in Ebola. As other actors define how they will contribute and coordinate regarding outbreak preparedness and response, and as Gavi reflects on the lessons learned so far in its part of the Ebola response, the question facing Gavi is what role, if any, it should play going forward?

There are four main areas with potential to leverage Gavi’s comparative advantage and existing programmes: (1) Gavi-supported vaccine stockpiles; (2) vaccines for outbreak diseases currently available, but outside of Gavi’s scope; (3) vaccines in development for emerging infectious diseases; and (4) country public health capacity building.

Context
The recent outbreaks of Ebola (and Zika), amongst other diseases, have refocused the world’s attention on the threat of infectious diseases with epidemic and pandemic potential, and countries’ preparedness to prevent, detect, and respond to them. Furthermore, a variety of factors – urbanization, increasing interconnectedness of populations through travel, migrant and refugee movement, climate change, and increasing human-animal interactions as communities expand – will continue to contribute to the frequency and reach of epidemics. Experience has shown that developing countries are likely to be the source of epidemics and bear the brunt of their impact.

In light of these concerns, there is growing attention on global health security. A number of initiatives have been launched or proposed to improve coordination and financing; including development of health technologies such as vaccines to combat emerging pathogens (see Supplementary Annex E). While vaccines are only one element of a broader coordinated strategy for outbreak diseases, they can play a critical role.
While Gavi is not an emergency response organization, it is already engaged in preparedness and response for disease outbreaks in several ways. Gavi funds vaccine procurement to address outbreaks through the creation and deployment of stockpiles (e.g., meningococcal A; meningococcal A,C,Y,W; yellow fever; cholera) and immunization campaigns to respond to outbreaks (e.g., measles). Gavi also contributes to the development of public health capacity through its health systems strengthening (HSS) investments and routine immunization programmes. When the Ebola epidemic struck, the world turned to Gavi to help ensure basic immunization services were maintained or re-established in the affected countries and for help in bringing forth a vaccine. Gavi responded, including securing a commitment from a manufacturer for the continued development and future availability of an Ebola vaccine.

Gavi will present some questions it is currently considering.

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Systems Vaccinology: Probing the Human Immune System with Vaccines
Bali Pulendran, PhD
Emory Vaccine Center
Emory University
Atlanta, GA

Objective: Explain how two recent developments might increase understanding on how our vaccines stimulate the protective immune response.

Abstract: Despite their great success, we understand little about how effective vaccines stimulate protective immune responses. Two recent developments promise to yield such understanding: the appreciation of the crucial role of the innate immune system in sensing microorganisms and tuning immune responses, and advances in systems biology. In this presentation, I will discuss how these developments are yielding insights into the mechanism of some of the most successful vaccines ever developed. Furthermore, such developments promise to address a major challenge in vaccinology: that the efficacy of a vaccine can only be ascertained retrospectively, upon infection. The identification of molecular signatures induced rapidly after vaccination, which correlate with and predict the later development of protective immune responses, would represent a strategy to prospectively determine vaccine efficacy. Such a strategy would be particularly useful when evaluating the efficacy or immunogenicity of untested vaccines, or in identifying individuals with sub-optimal responses amongst high risk populations, such as infants or the elderly. We have recently used a systems biology approach to identify early gene signatures that correlate with, and predict the later immune responses in humans vaccinated with the live attenuated yellow fever vaccine YF-17D, or with the influenza vaccines. I will review these studies, and discuss their broader implications for vaccinology.
**Objective:** Discuss special considerations relevant to dengue vaccines, approaches being used to develop dengue vaccines, recent clinical experiences with leading candidates, and public health implications.

**Abstract:** Millions of people living in tropical and subtropical parts of the world are infected by dengue viruses (DENV) each year. Several hundred thousand of these infections, especially in children, progress to dengue hemorrhagic fever, which is a life-threatening disease. Adaptive immunity, especially antibody, is critical for protection from DENVs. Under some conditions, DENV-specific immunity can enhance viral infection and exacerbate disease. As the DENV complex has 4 virus serotypes, a successful vaccine should induce balanced and protective immunity to all 4 serotypes. While many different approaches are being used to develop dengue vaccines, the leading candidates in clinical trials are based on tetravalent live attenuated flavivirus formulations. A chimeric yellow fever/dengue tetravalent live vaccine developed by one manufacturer has completed the active phase of efficacy trials in Asia and Latin America. Vaccine efficacy varied by serotype, with higher efficacy rates against serotypes 3 and 4 than against serotypes 1 and 2. Furthermore, efficacy was higher in participants who had been previously exposed to dengue than in participants who were dengue-naïve at baseline. These results underscore both the promise and complexity of dengue vaccine development.

The field of dengue vaccines is hampered by the lack of well-defined correlates and mechanisms of protective immunity. Recent studies with people exposed to natural DENV infections have led to the identification of new epitopes linked to protective immunity. These natural infection studies are foundational to understanding vaccine responses and improving vaccine design and use. Over the next decade we will see the introduction multiple vaccines for the prevention and control of dengue.

**References:**


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**Application of Biotechnology in Emergency Poultry Vaccines for Highly Pathogenic Avian Influenza**

David E. Swayne, DVM, PhD

US National Poultry Research Center
Agricultural Research Services
US Department of Agriculture
Athens, GA

**Objectives:** List the basic components of high pathogenicity avian influenza (HPAI) control and eradication programs in the US and the world for the 39 HPAI poultry epizootics. Learn how vaccines can be used as a tool in HPAI control and eradication. Describe the practical biotechnologies used to develop the emergency vaccine bank for US poultry.
Abstract: Since 1959, there have been 39 epizootics of high pathogenicity avian influenza (HPAI) in poultry of the world with 34 of 39 epizootics using stamping-out programs only, leading to rapid eradication. Five of the epizootics have used vaccines as a means to control the disease and reduce infection pressure and spread of the disease, along with stamping-out programs. The US developed an emergency vaccine bank for poultry in response to the H5Nx HPAI outbreak of 2014-15, using the latest biotechnologies including reverse genetic H5N1 low pathogenic avian influenza (LPAI) viruses for inactivated vaccines (rgH5N1), recombinant herpesvirus of turkeys with H5 hemagglutinin gene insert (rHVT-H5) and replication-defective RNA particle vaccine with H5 hemagglutinin gene insert (RNP-H5). The rgH5N1 and RNP-H5 contain the clade 2.3.4.4 H5 hemagglutinin gene insert from the outbreak virus, but changed to the LPAI virus proteolytic cleavage site, and the rHVT-H5 the hemagglutinin from an earlier Clade 2.2 H5 HPAI virus. Initial studies indicated the historic USDA H5 vaccine bank strains, using naturally occurring H5 LPAI viruses could provide protection from mortality, but varied greatly in their ability to reduce the number of poultry and the quantity of oral and cloacal replication and shedding of challenge virus. Among all experiments, the rgH5-inactivated vaccine (Clade 2.3.4.4) gave the best results in preventing mortality and reducing North American Clade 2.3.4.4 HPAI challenge virus replication and shedding in chickens and turkeys, either in single or prime-boost vaccination regimes. The rHVT-H5 (Clade 2.2) and RNP-H5 (Clade 2.3.4.4) worked best in a priming vaccine application followed by booster vaccinations with rgH5-inactivated or RNP-H5 vaccines. The reduction in virus shedding was associated with hemagglutination inhibiting antibodies and were evident for more than 6 months after a prime-boost regime of rgH5N1 vaccine. In young birds, the RNP-H5 may require a higher vaccine dose for optimal protective response. In ovo applications are most promising with rHVT-H5. Collectively, studies support a prime-boost regime for initial optimal protection.

References:

Zika Vaccine Development
COL Paul B. Keiser, MD
Walter Reed Army Institute of Research
Silver Spring, MD

Objectives: Discuss current Zika virus vaccine candidates. Describe Zika virus vaccine target profiles. Explain the lessons learned from other flavivirus vaccine development efforts.

Abstract: Zika virus (ZIKV) is a flavivirus first isolated from a non-human primate and Aedes mosquito species in 1947-48; shortly thereafter it was isolated from human beings. ZIKV transmission and human disease has been documented in Africa and Asia with periodic and episodic frequency since its discovery. In 2007, on the Micronesian Island of Yap, there was a large outbreak with significant human disease providing a view into this arboviral disease’s epidemic potential. The current Zika outbreak has gripped the world’s attention due to the kinetics of spread from Asia to and throughout the Americas and its potential causal association with increased rates of Guillain-Barré syndrome and microcephaly. Significantly reducing human infection and disease rates through vector control requires great expertise, informed application, resources, and perseverance. Developing effective anti-virals for diseases with short incubation times and periods of viremia is equally challenging. There is precedence for the successful prevention of flaviviral disease through active immunization utilizing a diverse range of constructs. Live attenuated virus vaccines have been licensed for Yellow fever, Japanese encephalitis, and dengue while inactivated vaccines have been developed for Tick Borne encephalitis and Japanese encephalitis. Defining the target product profile for a ZIKV vaccine is a complex exercise due to the potential neurologic and maternal-fetal implications of infection making the target population for vaccination broad and with an increased safety risk. ZIKV vaccine candidates and their relative strengths and challenges will be discussed. ZIKV vaccine target product profiles will be proposed. Lessons learned from other flavivirus vaccine development efforts will be discussed.
Chikungunya Vaccine Development
Barney S. Graham, MD, PhD
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Objectives: Discuss the status of Chikungunya in the Americas. Review options for vaccine development, focusing on the virus-like particle (VLP) approach that is now in phase II testing.

Abstract: Chikungunya virus (CHIKV) is a mosquito-borne alphavirus in the family Togaviridae that causes a febrile, systemic illness associated with disabling polyarthralgias. CHIKV is a global public health threat for which a preventive vaccine is needed. CHIKV was isolated from a member of the Makonde tribe in Tanzania in 1952, and identified at the East African Virology Research Institute (now the Ugandan Virology Research Institute). CHIKV re-emerged in a 2005 epidemic that started in Kenya then spread across the Indian Ocean and propelled by a specific mutation in the E1 protein that increased viral infectivity of the Aedes albopictus vector that enabled broader dissemination of CHIKV. Near the end of 2013, CHIKV was introduced to the Caribbean and has infected ~2 million people spreading also to Mexico and many countries in Central and South America. While CHIKV is primarily transmitted by Aedes aegypti in the Caribbean, adaptation to Aedes albopictus could lead to a more wide spread epidemic in more temperate zones of the Western hemisphere including the US

Vaccine development efforts have included live-attenuated vaccines which were immunogenic but accompanied by arthralgia in clinical trials; recombinant MVA, measles, and adenovirus vectored vaccines; a chimeric alphavirus vaccine; DNA vaccines; whole-inactivated virus; and virus-like particles (VLP). VLP vaccines consist of self-assembled viral structural proteins that mimic the surface of wild-type virus. By simulating the antigenicity of mature infectious virus and displaying epitopes in an ordered high-density array, VLP vaccines are highly immunogenic and induce high quality neutralizing antibody. VLPs are safe because they are non-replicating and non-infectious. Because live virus is not utilized in manufacturing, viral attenuation or inactivation is unnecessary and manufacturing can be done in low containment facilities.

Expression of the CHIKV structural proteins (C-E3-E2-6K-E1) from the West African CHIKV stain 37997 results the production of VLPs that resemble wild-type virus with E1 and E2 glycoproteins organized into heterodimers. Pre-clinical testing of this VLP in non-human primates showed that it induced neutralizing antibody to both homologous and heterologous CHIKV strains and provided protection from viremia in a live CHIKV challenge model. In Phase I testing the vaccine was well tolerated and without dose limiting toxicity. Subjects received a three-dose regimen of 10, 20, or 40 mcg at weeks 0, 4, and 20 by intramuscular injection. All subjects developed robust neutralizing antibody titers following the first or second vaccination as well as durable humoral responses that persisted at least 6 months following completion of the regimen. Neutralizing antibody titers reached levels inferred to be protective following natural infection by comparison to human convalescent neutralizing antibody responses in the same assay. This product is in Phase II evaluation in a randomized, placebo-controlled trial in CHIKV endemic regions of the Caribbean using a two dose regimen of 20 mcg.

References:
Pathways of Induction of HIV Broadly Neutralizing Antibodies
M. Anthony Moody, MD
Duke Human Vaccine Institute
Duke University Medical Center
Durham, NC

**Objective:** Explain the new strategies currently being tested to elicit bnAbs by multiple vaccine candidates.

**Abstract:** Human immunodeficiency virus (HIV) remains a global health threat, accounting for more than 1 million deaths every year. While development of an effective HIV vaccine has been a research priority, an effective vaccine remains elusive because of the ability of HIV to mutate and evolve to a greater extent than many other human pathogens in addition to its ability to integrate into the infected person’s genome. One strategy for a successful HIV vaccine is to induce antibodies that can recognize and neutralize the majority of HIV quasi-species, called broadly reactive neutralizing antibodies (bnAbs). These antibodies target the HIV outer coat protein or envelope (Env) and recognize a number of conserved regions on Env that allow them to bind to different HIV strains. However, bnAbs only arise in some HIV-infected persons after years of HIV infection. Vaccines with Env proteins that express conserved bnAb targets (epitopes) have not successfully induced bnAbs after vaccination. Study of bnAbs and viruses from infected persons has defined bnAb epitopes and has revealed unique characteristics of bnAbs required for neutralization. One current approach being pursued by our team is to define the events that transpire during HIV-1 infection and then to recreate these events with a vaccination regimen. This has led to the development of new strategies currently being tested to elicit bnAbs by multiple vaccine candidates.

Broadly Neutralizing Antibodies and HIV Vaccine Design
Dennis Burton, PhD
Scripps Research Institute
La Jolla, CA

**Objective:** Discuss the challenges using broadly neutralizing antibodies in HIV vaccine design.

**Abstract:** Broadly neutralizing antibodies (bnAbs) represent a variety of solutions to recognition of a difficult target—the HIV envelope spike—that can be achieved given the chronic nature of HIV infection. The challenge is how to translate knowledge of these Abs and their evolution into immunogens and, importantly, to find ways to evaluate whether the immunogens are driving appropriate Ab responses. These challenges will be discussed.

**Reference:**

Broadly Neutralizing Antibodies for Treatment of HIV Infected Patients
Marina Caskey, MD
The Rockefeller University
New York, NY

**Objective:** Discuss anti-HIV broadly neutralizing antibodies that are in clinical development and their potential applications in HIV treatment as adjuncts to standard antiretroviral therapy or as part of eradication strategies.

**Abstract:** Despite the major success of combination antiretroviral therapy (ART) in suppressing viral replication and preventing disease progression, HIV-1 infection persists and is not eliminated by available antiretroviral drugs. When ART is discontinued, viral rebound occurs within 2-3 weeks in most subjects. Broadly neutralizing antibodies differ from other therapeutic modalities for HIV-1 infection in several respects. First, they can neutralize the pathogen directly; second, they have the potential to clear the virus and infected cells through engagement of innate effector responses; and third, immune complexes produced by the passively transferred
antibodies may enhance immunity to HIV-1. In addition, since antibodies have far longer half-lives than currently used antiretroviral drugs, they might allow for more convenient therapeutic regimens. Therefore, broadly neutralizing antibodies might have a role as adjuncts to ART, in stand-alone maintenance treatment regimens or in strategies that aim to eradicate HIV-1 or to induce long-term ART-free HIV-1 remission.\(^1\) 3BNC117 and 10-1074 are two anti-HIV-1 broadly neutralizing antibodies that target the CD4 binding site and the base of the V3 loop within HIV-1 envelope gp-120, respectively. When tested against large HIV-1 pseudovirus panels, including multiple clades, 3BNC117 neutralizes more than 80% of the viral isolates and 10-1074 neutralizes between 60 and 70%. Against sensitive strains, 10-1074 is more potent than 3BNC117.\(^2,3\) They were selected for clinical development for their in vitro neutralizing breadth and potency and for their antiretroviral activity in humanized mice (hu-mice) and non-human primate models (NHP).\(^4,5\) In humans, both 3BNC117 and 10-1074 were generally safe and well tolerated at doses up to 30 mg/kg. 3BNC117 and 10-1074 half-lives were approximately 2 weeks in HIV-uninfected and about 10 days in viremic HIV-infected individuals. Both 3BNC117 and 10-1074 induced rapid decreases in plasma HIV-1 RNA levels, with average decline in plasma viremia of 1.48 and 1.35 log\(_{10}\) copies/ml, respectively. Selective pressure on circulating viruses was observed after administration of either 3BNC117 or 10-1074.\(^6\) Ongoing and planned clinical studies will evaluate their effect on the HIV-1 latent reservoir and their ability to maintain viral suppression in the absence of ART.

References:


Broadly Neutralizing mAbs and Vaccine Antigens for HIV
Barney S. Graham, MD, PhD
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Objective: Discuss the current options for passive and active immunization to prevent HIV infection, focusing on approaches based on protection through neutralizing antibody activity.

Abstract: VRC01 is one of the first broadly neutralizing HIV-specific monoclonal antibodies to enter clinical evaluation. It is an HIV-1 CD4 binding site-specific monoclonal antibody (mAbs) with potent and broad neutralizing activity. Phase I studies have been performed in HIV-uninfected adults and infants and HIV-infected adults. Data have been generated on dose, route, regimen, safety, pharmacokinetics (PK), and virological activity. No serious adverse events or dose-limiting toxicity have been noted in HIV-infected or uninfected subjects, and 28 day trough serum concentrations were 34.9±6.5 and 57.2±19.0 mcg/mL after the first IV infusion, and 55.9±16.8 and 88.8±40.4 mcg/mL after the second, respectively. VRC01 retained broad NT activity in serum and anti-VRC01 responses have not been detected. Ongoing studies include the PK evaluation of extended half-life variants (VRC01-LS) or delivery of a clonal family member (VRC07) delivered by gene transfer from AAV8. Therapeutic potential of VRC01 to diminish viremia during acute infection, provide maintenance therapy in combination with long-acting anti-retroviral drugs, or reduce viral reservoir during chronic infection is also being evaluated. Second generation CD4 binding site-specific mAbs with higher potency and breadth and extended
half-life are being explored for use as single agents or in combination with mAbs to other neutralizing sites for prevention and treatment.

Recent advances in elucidating the full trimer structure for HIV-1 Env, and using broadly NT mAbs to guide engineering efforts to stabilize and expose neutralization-sensitive surfaces, has led to a series of new HIV immunogen designs and promise improved vaccine antigens for future active immunization studies.

References:

Prioritization of Diseases for Which Vaccines Could Reduce Antimicrobial Use in Animals
Elisabeth Erlacher-Vindel, PhD
World Organisation for Animal Health (OIE)
Paris, France

Objective: Explain what the expectations of the World Health Organisation for Animal Health (OIE) are regarding vaccine development.

Abstract: Antimicrobial resistance is a global human and animal health concern that is influenced by the use of antimicrobial agents in both human and veterinary medicine, as well as in the plant sector. To combat antimicrobial resistance, the World Organisation for Animal health (OIE) has developed science-based intergovernmental standards and guidelines covering terrestrial animals and aquaculture.

The OIE also contributed to the development of the WHO Global Action Plan on Antimicrobial Resistance, adopted in 2015 by the World Health Assembly. The 180 Member Countries of the OIE expressed their support to this plan of action through a Resolution, unanimously adopted in May 2015.

As a contribution to the global actions to address antimicrobial resistance, and in consideration of the use of vaccines to prevent diseases as one of the possible options to reduce the use of antimicrobial agents at the global level, the OIE convened an ad hoc Group on Prioritisation of Diseases for which Vaccines could Reduce Antimicrobial Use in Animals in April 2015.

Animal diseases for which availability and use of vaccines could reduce the use of antimicrobial agents in animals were identified and recommendations were made to better target research programmes for new or improved vaccines. The Group focused on pigs, poultry, and fish as a first step and reviewed the main reasons for antibiotic use. Key diseases, including some viral diseases, driving antibiotic use in animals were considered, and areas for research, where investment could lead to new or improved vaccines with the potential to reduce antibiotic use were identified.

The outcome of this work, which will be presented in detail, was the development of tables of ranked priority diseases per species considered with the aim of providing direction to policy makers and research communities on where to invest to reduce the need for antimicrobial use in animals with a focus on vaccines.
Objective: Discuss the impact that *H. influenzae* type b vaccine and *S. pneumoniae* vaccines have had on antibiotic resistance and review the progress towards a *S. aureus* vaccine.

Abstract: Before the universal deployment of the *H. influenzae* type b vaccine, resistance to ampicillin and chloramphenicol represented formidable clinical problems. In a similar vein, penicillin resistance in *S. pneumoniae* was a special clinical problem as resistance was high among isolates that caused clinical disease.

The case of *S. aureus* infection is of particular interest. This species, a major human pathogen, has been the cause of multiple clinical syndromes. Despite repeated attempts to formulating an active vaccine or a passive vaccine, we are rather far from understanding what a successful vaccine candidate would consist of.

The epidemiologic case for a universal vaccine is strong. The species is often surrounded by a polysaccharide capsule. Despite this and despite the immunogenicity of the purified capsular polysaccharide when conjugated to *P. aeruginosa* exotoxoid A, it is clear that antibodies directed against the capsule are not protective and that species members do not need a capsule to cause clinical infection. Moreover, it is not clear that the same antigens protect against all clinical syndromes cause by this species.

It is also not clear that the production of opsonophagocytic antibody will produce protection. Recently, antigens have been identified by production of certain cell mediated cytokine products. Thus, even the mechanism of action of a viable candidate *S. aureus* vaccine is open to question and may involve the production of certain cytokines.

References:

Development of Vaccines to Prevent *Clostridium difficile* and *Campylobacter jejuni* Infections

Mario A. Monteiro, PhD
University of Guelph
Guelph, ON
Canada

Objective: Explain how to search and discover bacterial polysaccharides and how to synthesize and characterize polysaccharide conjugate vaccines.

Abstract: Our research efforts focus on the discovery and use of microbial-specific polysaccharides to control gastric bacterial infections in humans. Two of our targets are *Clostridium difficile* (antibiotic associated diarrhea) and *Campylobacter jejuni* (traveller’s diarrhea).
Using a combination of physico-chemical methods we extracted, purified and characterized cell-surface polysaccharides of *C. difficile* and *C. jejuni* and used them in conjugate vaccine preparations.

We discovered that *C. difficile* and *C. jejuni* produce distinctive cell-wall polysaccharides that when integrated into vaccine formulations were capable of eliciting antibodies that prevented the corresponding disease in animal models.1-2 *C. difficile* ribotypes were found to expose a common polysaccharide (named PS-II) composed of hexasaccharide phosphate repeating blocks. After its discovery, PS-II quickly attracted the attention of many researchers as a *C. difficile* vaccine target. In our hands, a PS-II conjugate vaccine protected about 90% of mice challenged with *C. difficile* spores.4 In the case of *C. jejuni*, a multivalent approach was needed, as each serotype complex expressed a specific polysaccharide. The prototype *C. jejuni* polysaccharide-based vaccine was shown to fully protect against *C. jejuni* diarrhea in a monkey model4 and preliminary data from a phase 1 clinical trial has demonstrated its safety in humans. Recently, we have discovered that certain regions of *C. jejuni* polysaccharides containing methyl phosphoramidate (MeOPN) linkages are highly immunogenic.5 A MeOPN galactose synthetic construct (left) reacted with antisera from *C. jejuni* serotypes containing MeOPN at primary positions, and was found to have more bactericidal activity than the native polysaccharide vaccine.

The gastric pathogens *C. difficile* and *C. jejuni* expose specific cell-wall polysaccharides that when converted into glycoconjugate vaccines are capable of fighting the corresponding bacterial infection in animal models. Such polysaccharide based vaccines have the potential to control disease and colonization.

References:


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**Clinical Trials of Vaccines Administered During Pregnancy**

Flor Munoz-Rivas, MD
Baylor College of Medicine
Houston, TX

**Objectives:** Explain the concept of maternal immunization as a strategy to prevent infectious diseases in mothers and infants. Discuss the rationale and methodology associated with studying vaccines for administration during pregnancy.

**Abstract:** Immunization of women during pregnancy is an accepted strategy to protect mothers and infants against infectious diseases during a period of high vulnerability. As a public health intervention, maternal immunization has the potential to reduce the morbidity and mortality associated with pathogens that affect the mother, the newborn, or both. Maternal immunization with tetanus, pertussis and influenza vaccines results in direct protection of the mother and the newborn infant. Group B streptococcus and Respiratory Syncytial Virus (RSV) are infections that could be prevented through immunization of pregnant women with safe and effective vaccines that are currently under clinical investigation. The rationale, safety, effectiveness, acceptability, and potential impact of vaccination of women during pregnancy will be reviewed in this presentation. Challenges associated with the development and implementation of clinical trials of vaccines administered during pregnancy will be discussed.
References:

Safety Monitoring in Immunization in Pregnancy Efforts at NIH
Richard L. Gorman, MD
National Institute of Allergy and Infectious Diseases
Bethesda, MD

Objective: Review safety monitoring in maternal immunization studies sponsored by DMID/NIH, and how these efforts may align with the tools developed by the GAIA consortium.

Abstract: Key knowledge gaps identified during DMID sponsored studies were addressed by subject matter experts during consensus-building conferences. The output from these discussions were toxicity grading tables for laboratory tests, and adverse events grading tables of pregnancy and neonatal outcomes. Although overlapping in the topics of interest, DMID and GAIA efforts differ in the scope. DMID Tables do not provide ontology of terms and definitions, or the assessment of diagnostic certainly, that is especially relevant for studies in MLICs. Standardized definitions and tools to evaluate and report 21 most critical adverse events in pregnancy and neonatal period are provided by the GAIA consortium. Thus, GAIA and NIH efforts are complementary and if combined could improve quality of data generated in clinical trials, harmonize reporting and facilitate meta-analyses across multiple studies.

Reference:

NVAC Initiatives
Saad B. Omer, MBBS, MPH, PhD
Emory University
Atlanta, GA

Objective: Discuss updates on recent National Vaccine Advisory Committee (NVAC) initiatives regarding maternal immunization

Abstract: NVAC is working to identify barriers to and opportunities for developing vaccines for pregnant women and make recommendations to overcome these barriers. There are several current scientific and structural barriers for developing vaccines and countermeasures for pregnant women.1

One barrier is a lack of a broadly accepted ethical framework for guiding clinical research in pregnancy. Therefore, IRBs often resort to categorizing most intervention research in pregnancy as high risk, often without a balanced consideration of the risks of not performing the research. Hence, there is a need for development and articulation of a pregnancy specific ethical framework that can offer guidance to investigators and IRBs.
Pregnancy is a physiologically dynamic state. The immune profile of a pregnant woman is responsive to the changing levels of sex hormones, and evolves through the course of pregnancy. However, the current knowledge base for vaccine response draws from observational studies mostly conducted in the latter part of pregnancy, with limited data available from the first and early second trimester. On the other hand, clinical, practical and public health considerations require that vaccine use not be restricted to advanced gestational age.

Robust safety evaluation is a cornerstone of any vaccine development and deployment program. While there has been increased attention on evaluation of safety of immunization in pregnancy, barriers remain. For example, a review commissioned by the WHO highlighted that there is a lack of standard definitions of outcomes, and standards for measurement of these outcomes, relevant to evaluation of vaccines in pregnancy. This lack of standardization poses a challenge for conduct of clinical trials, generalizability of safety data, and the merging of large safety datasets. This last point is critical because large multi-location datasets would optimize the evaluation of rare but clinically important outcomes, such as microcephaly.

References:

Maternal Immunization: Perspective of PATH
Niranjan Bhat, MD, MHS
PATH
Seattle, WA

Objective: Discuss opportunities and challenges in the implementation of maternal immunization programs in limited-resource settings.

Abstract: The greatest burden of severe influenza and pertussis in children occurs during the first few months of life, yet vaccines against these diseases are not effective at that age. Immunization of pregnant women against both influenza and pertussis, however, has been shown to be effective in protecting infants. These interventions have therefore been recommended by global policy makers, yet their adoption in most countries has been slow, particularly in low-resource settings. Major reasons for this include a lack of quality data regarding disease burden and the impact of the intervention, uncertainties regarding the programmatic feasibility, regulatory and legal constraints, and low levels of awareness. This presentation will discuss many of the opportunities and challenges for implementing maternal immunization programs in low-income countries, and current efforts to address them.

References:
Objective: Articulate FDA regulatory perspective and regulations regarding clinical development of vaccines used in pregnancy

Abstract: There has been recent renewed interest in maternal immunization to protect the mother and infants from vaccine-preventable diseases. As an example, inactivated influenza vaccines have been recommended for use in women during all stages of pregnancy in numerous countries. In addition, tetanus, diphtheria, and acellular pertussis (TdaP) vaccines are recommended for use in pregnant women as an approach to reduce the burden of pertussis disease in infants less than 6 months of age. In addition, investigational vaccines such as vaccines to protect against respiratory syncytial virus, and group B Streptococcus (GBS) are in clinical development to protect the newborn and infant from infectious diseases. From a US FDA perspective, pre-licensure studies to evaluate the effectiveness of a vaccine used during pregnancy to protect the infant are needed for the prescribing information to include an indication and usage statement that describes such use. However, clinical development programs with investigational vaccines and/or with vaccines already licensed and recommended for use in pregnancy raise some complex issues. The purpose of this presentation is to discuss regulatory considerations for clinical safety and effectiveness evaluations for vaccines indicated for use in pregnancy. In addition, this presentation will summarize the deliberations of a recently convened Vaccines and Biologic Products Advisory Committee (VRBPAC) regarding clinical studies and study designs to demonstrate safety and effectiveness of vaccines used in pregnancy to protect the young infant, use of surrogate markers to infer effectiveness, safety evaluation and follow-up of mothers and infants as well as approaches to evaluating interference with regard to the immune response to vaccination among infants born to mothers immunized during pregnancy.

References:

SUBMITTED ORAL PRESENTATION ABSTRACTS
The Safety and Immunogenicity of a Parenterally Administered Modified Recombinant Staphylococcal Enterotoxin B Protein Vaccine


1Integrated BioTherapeutics, Inc., Gaithersburg, MD; 2Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, MD; 3Unither Virology, LLC, Silver Spring, MD

Objective: Cite the results of the first-in-man study of an attenuated Staphylococcal superantigen vaccine.

Background: Staphylococcal enterotoxins (SEs) are bacterial superantigens which bind to Class II major histocompatibility complex (MHC) proteins and T cell receptors (TCR) leading to massive polyclonal activation of T-cells. Exposures to Staphylococcal enterotoxin B (SEB) can precipitate clinical illnesses which can range from acute food poisoning to lethal toxic shock syndromes. SEB is also a category B select agent, because of the recognition that intentional aerosolization of minute amounts of SEB can result in marked incapacitation and death. There are currently no vaccines for Staphylococcus aureus or SEB. A recombinant SEB (rSEB) mutant, rendered deficient in MHC binding through mutations in the hydrophobic binding loop (L45R), the polar binding pocket (Y89A), and a disulfide loop (Y94A) within the MHC binding site, was developed using a structure-based rational approach. We conducted a first-in-man phase 1 dose-escalation study of rSEB administered with Alhydrogel (hereafter named STEBVax).

Methods: This single site first-in-man dose-escalation study was designed to assess the safety and immunogenicity of parenterally administered STEBVax with doses ranging from 0.01 mcg to 20 mcg. The study is registered as ClinicalTrials.gov number NCT00974935. Following vaccination, participants were observed in-clinic for eight hours and 14 days of reactogenicity was recorded. Immune responses were evaluated by serum anti-SEB total IgG and neutralizing antibodies. An independent Safety Monitoring Committee reviewed existing safety data prior to each dose escalation.

Results and Conclusion: A total of 28 eligible volunteers were enrolled in this study, with 4 participants distributed in each of 7 cohorts. There were no serious or severe adverse events related to vaccination observed. There were few solicited systemic and local reactions; those that occurred were mild or moderate in severity and were self-limited. Robust immune responses to vaccination as determined by serum anti-SEB total IgG and neutralizing antibodies were detected in higher vaccine doses. These data document a lack of safety concerns in this small sample of individuals vaccinated with STEBVax. The elicitation of antibody responses without toxicity is reassuring for the continued clinical development of STEBVax.

References:
compared with EB in adults. HEPLISAV-B combines hepatitis B surface antigen (HBsAg) with 1018, a toll-like receptor 9 (TLR9) agonist comprised of a 22-mer cytidine-phospho-guanosine oligonucleotide.

**Methods:** In a multicenter, observer-blinded Phase III study, 8,374 participants 18-70 years of age were randomized 2:1 to receive HEPLISAV-B (20μg rHBsAg combined with 3000μg 1018) given at Weeks 0 and 4 (placebo at Week 24) or EB given at Weeks 0, 4, and 24. A primary objective was to compare the safety of the vaccines with respect to clinically significant adverse events. A secondary objective was to determine if the immunogenicity of 2 doses of HEPLISAV-B is non-inferior/statistically significantly higher to 3 doses of EB by comparing peak seroprotection rates (SPR = anti-HBs ≥ 10mIU/mL).

**Results and Conclusion:** Complete trial results will be available in February 2016. Overall safety results for medically-attended adverse events, serious adverse events, deaths, and immune-mediated adverse events will be presented. Immunogenicity results will include comparisons of peak SPRs and anti-HBs geometric mean concentrations between HEPLISAV-B and EB. The immunogenicity and safety of two doses of HEPLISAV-B were compared with the standard three-dose regimen of Engerix-B in a large study of adults 18 to 70 years of age.

**References:**

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**Safety and Immunogenicity of H7 Influenza Prime-Boost Regimens in Healthy Adults**

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1NIH/NIAID/Vaccine Research Center, Gaithersburg, MD; 2NIH, Bethesda, MD; 3National Institutes of Health/Vaccine Research Center, Springdale, MD; 4National Institutes of Health, Rockville, MD; 5NIAID/National Institutes of Health, Clarksburg, MD; 6CDC, Atlanta, GA; 7NIH/NIAID/VRC, Bethesda, MD

**Objective:** Discuss the results of a Phase I study evaluating the safety and immunogenicity of a H7 DNA-H7N9 MIV prime-boost vaccine regimen in adults.

**Background:** A novel avian influenza subtype, A/H7N9, emerged in 2013 and represents a public health threat with pandemic potential. We have previously shown that DNA vaccine priming increases the magnitude and quality of antibody responses to H5N1 monovalent inactivated boost (MIV) when administered with a 12-24 week boost interval. We now report the safety and immunogenicity of a H7 DNA-H7N9 MIV prime-boost regimen.

**Methods:** VRC 315 was a Phase I, open label, randomized clinical trial evaluating three H7N9 prime-boost vaccination regimens in healthy adults. Group 1 received H7 DNA vaccine prime and H7N9 MIV boost. Group 2 received both H7 DNA and MIV as a prime and an MIV boost. Group 3 received H7N9 MIV in a homologous prime-boost regimen. The prime-boost interval was 16 weeks for all groups. The primary endpoints evaluated the safety and tolerability of the three prime-boost regimens. Secondary and exploratory endpoints evaluated H7-specific antibody responses assessed by hemagglutination inhibition assay (HAI) and neutralizing antibody assays.

**Results and Conclusion:** Overall, 13 (43.3%) males and 17 (56.7%) females with an age range of 20 to 60 years enrolled and 28 (93.3%) completed both vaccinations. All injections were well tolerated with no serious adverse events. Two weeks following the MIV boost, at least a four-fold increase in neutralizing antibody responses were seen in 90% of Group 1, 100% of Group 2 and 78% of Group 3 subjects. Peak neutralizing antibody geometric mean titers were significantly greater for Group 1 (GMT=440.61, p < 0.05) and Group 2 (GMT=331, p=0.02) when compared with Group 3 (GMT=86.11). Two weeks post-boost, 4 of 10 subjects in Group 1 and 3 of 9 subjects in Group 2 achieved a HAI titer > 1:40 compared with 1 of 9 subjects in Group 3. This novel H7 DNA vaccine was safe, well-tolerated and immunogenic when boosted with monovalent inactivated H7N9. Compared to MIV prime, the H7 DNA primed for higher HAI and neutralizing antibody titers detected 2 weeks following the MIV boost.
Efficacy of Recombinant Influenza Vaccine (Flublok® Quadrivalent, RIV4) versus Egg-Derived Inactivated Vaccine (IIV4) in Adults ≥50 During a Season Characterized by Antigenic Mismatch Between Circulating and Vaccine H3N2 Strains

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¹Protein Sciences Corporation, Meriden, CT; ²Bethesda Biologics Consulting, San Antonio, TX; ³Jean Brown Research Center, Salt Lake City, UT; ⁴Biologics Consulting Group, Inc., Alexandria, VA

Objective: Explain the improved efficacy of recombinant influenza vaccine (RIV4) against drifted and non-drifted influenza strains.

Background: Previous studies demonstrated that recombinant influenza hemagglutinin vaccines (RIV) induced particularly robust immune responses to influenza A/H3N2 subtypes and relatively high degrees of protective efficacy against antigenically drifted and non-drifted influenza strains.¹ ² We compared the protective efficacy and safety of (Flublok® Quadrivalent RIV4) versus an egg-derived IIV4 during the 2014-15 influenza season, described by CDC as moderately severe with high levels of influenza-associated hospitalization, especially for adults aged ≥65 years. The majority of the predominant circulating A/H3N2 viruses differed antigenically from the corresponding vaccine component.³

Methods: PSC12 was a randomized, observer-blinded trial of RIV4 vs. IIV4 comparing relative vaccine efficacy (rVE) against laboratory-confirmed, protocol-defined influenza-like illness (ILI) due to any influenza strain in adults ≥50 years of age. Nasopharyngeal swabs (NP) from subjects who reported ILI symptoms underwent rtPCR-testing and cell culture to confirm influenza infection. Immunogenicity was assessed in a subset of study participants.

Results and Conclusion: 9,003 subjects were enrolled and randomized; 8,605 subjects were followed throughout the influenza season. NP swabs from 1,628 subjects yielded 234 (14.4%) PCR-confirmed protocol-defined ILI, including 181 influenza A/H3N2, 47 influenza B and 6 non-typeable influenza A. The influenza attack rate was 2.2% (96/4303) in RIV4 and 3.2% (138/4301) in IIV4 recipients, yielding a rVE of RIV4 of +31% (95% CI 10, 47), that satisfied both the primary efficacy criterion for non-inferiority (lower bound of the 95% CI > -20%) and the pre-specified exploratory criterion for superiority of RIV4 over IIV4 (rVE lower bound of 95% CI > 9.0%) (p < 0.001). Attack rates of A/H3N2 were 1.7% vs. 2.7%, yielding an rVE for RIV4 of +37% (95% CI 14, 53) for PCR-positive and +45% (95% CI 22, 61) for culture-positive H3N2 ILI. Hospitalizations for influenza A and medical visits for ILI were less common among RIV4 than IIV4 recipients (n=7/4328 vs. n=16/4344, respectively), although not statistically different (p=0.09). Safety profiles of the vaccines were similar and HAI antibody responses to A/H3N2 were significantly higher among RIV4 recipients. Among adults ≥50 years of age, (Flublok® Quadrivalent RIV4) provided better protection against PCR-confirmed influenza illness versus an egg-derived IIV4 during a moderately severe A/H3N2-predominant influenza season of mostly antigenically mismatched A/H3N2 viruses.³ Health outcomes suggested reduced hospitalization and healthcare utilization for ILI among RIV4 recipients.

References:
Safety and Immunogenicity of Tetanus-Diphtheria-Acellular Pertussis Vaccine (Tdap) During Pregnancy
Dalhousie University, Halifax, Nova Scotia, Canada

Objective: Explain the antibody response to the primary pertussis vaccine series of infants whose mothers received Tdap during pregnancy.

Background: Immunization of women during pregnancy with Tdap is recommended to provide protection against pertussis to the newborn infant; however, this intervention has not been well studied.

Methods: We undertook a randomized, controlled clinical trial to measure the safety, reactogenicity, and immunogenicity of Tdap given during pregnancy, the transplacental passage of antibody, and the effect of maternal immunization with Tdap on the infant’s immune response to the primary immunization series with diphtheria-tetanus-acellular pertussis-inactivated-poliovirus-Haemophilus influenzae-b vaccine. A total of 273 women were enrolled in the study, randomly allocated to receive either Tdap or Td in the third trimester, delivered infants, and provided samples for the safety and immunogenicity analyses; 261 infants provided serum specimens for the immunogenicity analysis.

Results and Conclusion: Both Tdap and Td were well-tolerated during pregnancy; rates of adverse events were similar in both groups. There were 76 serious adverse events (29 for women, 47 for infants) uniformly distributed by group: 73 were unrelated; 2 were possibly related; 1 was probably related. Antibodies against pertussis toxin (PT), filamentous hemagglutinin (FHA), pertacin (PRN) and fimbriae (FIM) were elicited in the women and transferred across the placenta; infants of Tdap recipients had cord blood levels that were 21% higher than maternal levels for PT, 13% higher for FHA, 3% higher for PRN, and 7% higher for FIM. Infants whose mothers received Tdap during pregnancy had significantly higher PT antibody levels at birth and 2 months of age (pre dose 1) and significantly higher FHA, PRN, and FIM antibodies at birth, 2, and 4 months of age (pre doses 1 and 2). Infants of Tdap immunized mothers had significantly lower PT and FHA antibody levels at 6 and 7 months of age and significantly lower PRN and FIM antibody levels 7 months of age. At 7 months, the Tdap/Td antibody ratio for infants was 0.74 for PT, 0.60 for FHA, 0.59 for PRN, and 0.40 for FIM. This study demonstrated that Tdap is well-tolerated during pregnancy and results in higher levels of antibodies early in infancy but lower levels after the primary series. The higher levels at birth may provide protection during the highest risk of severe pertussis in the immediate postnatal period but this may be at the expense of increased susceptibility during the second half of the first year of life.

References:

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GEN-003, a Therapeutic Vaccine for Genital Herpes, Significantly Reduces Anogenital Lesion Rates and Mucosal HSV-2 Shedding
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Genocea Biosciences, Cambridge, MA

Objective: Describe the safety and efficacy of GEN-003, a novel herpes immunotherapy, in patients with recurrent genital herpes.

Background: Genital herpes is a lifelong infection associated with repeated outbreaks of painful genital ulcers and significant psychological distress. Daily antiviral treatment reduces outbreaks, but has only moderate effect on transmission. Episodic treatment, taken by majority of patients, has no effect on asymptomatic shedding between outbreaks, which is believed to the source of most new infections. Multiple previous efforts to develop vaccines for herpes, usually focused on eliciting antibody, have met with failure. GEN-003, a genital herpes
immunotherapy, was developed using ATLAS™, a high throughput system that identified HSV antigens associated with cellular immune responses in exposed seronegative and asymptomatic seropositive patients. GEN-003 contains two antigens, glycoprotein GD, which also contains the major epitopes for neutralizing antibody, and a fragment of the immediate early protein ICP4. These are combined with Matrix-M2, a saponin-based adjuvant (Novavax, Inc.).

**Methods:** Two clinical studies have been conducted to date enrolling otherwise healthy HSV-2 infected individuals, age 18-50, experiencing 3-9 genital herpes outbreaks annually. Subjects were immunized with various dose combinations of antigens (10 – 100 μg) and adjuvant (0-75 μg). Endpoints included safety, humoral, and cellular immunogenicity, and genital lesion rates and mucosal shedding rates before and at various timepoints after vaccination. Shedding was measured by change in percent positive swabs by HSV-2 PCR. Changes in shedding and lesion rates were analyzed using a Poisson mixed effects model.

**Results and Conclusion:** Treatment with GEN-003 resulted in over 50% reduction in mucosal HSV-2 shedding continuing at least 6 months after immunization and similar reduction in genital lesion rates for many dose combinations tested. Both cellular and humoral immune responses persisted at least 12 months. GEN-003 was moderately reactogenic, but side effects appeared to decrease with subsequent immunizations and were not associated with increased rates of discontinuation. There have been no related serious adverse events, autoimmune events or other adverse events of special interest. GEN-003 is a novel herpes immunotherapy associated with clinically relevant reductions in herpes lesions and asymptomatic mucosal shedding. Future plans include continued development as a herpes immunotherapy and evaluation for potential as a prophylactic vaccine.

**References**


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**Adverse Events Following DTaP Vaccination in the Vaccine Adverse Event Reporting System**

**P. L. Moro, P. Lewis, M. Cano**

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**Objectives:** Describe the main adverse events after DTaP vaccines reported in the Vaccine Adverse Event Reporting System (VAERS). List the strengths and limitations of spontaneous reporting systems such as VAERS for monitoring adverse events after vaccination. Explain the types of analysis used to assess the safety of DTaP vaccines in a spontaneous reporting system such as VAERS.

**Background:** In 1997, ACIP recommended DTaP for all five doses in the childhood vaccination schedule. There are currently five DTaP vaccines used in the United States: (Daptacel®, Infanrix®, Kinrix®, Pediarix®, Pentacel®). Few post-licensure studies have been conducted to assess the safety of these vaccines. The objective of this study was to assess the safety of DTaP vaccines in VAERS during 1/1/1997–7/31/2015.

**Methods:** We searched the VAERS database for US reports of adverse events (AEs) among persons who received DTaP during 1/1/1997–7/31/2015. All reports of death were reviewed, and we reviewed a random sample of reports and accompanying medical records for non-death serious reports (life-threatening illness, hospitalization, prolongation of existing hospitalization, or permanent disability). Physicians assigned a primary clinical category to each reviewed report.

**Results and Conclusion:** During the study period VAERS received 46,441 reports following DTaP vaccination; 5,201 (11%) were coded as serious which included 793 deaths. The most frequent cause of death was sudden infant death syndrome [SIDS] (338; 49.6%). 44,061 (95%) reports involved children aged < 6 years. DTaP vaccines
were administered concurrently with one or more other vaccines in 40,868 (88%) reports. The median time from vaccination to onset of an AE for both serious and non-serious reports was 1 day. The most frequently reported AEs were injection site erythema (11,879; 26%), pyrexia (9,225; 20%), injection site swelling (6,964; 15%), erythema (5,339; 12%), and injection site warmth (4,468; 10%).

Review of VAERS reports did not identify any new or unexpected safety concerns for DTaP vaccines. The reported causes of death are consistent with those for US infants, among whom SIDS is the fourth leading cause but is the leading cause that is not present/cannot be identified at birth.

References:

Surveillance of Adverse Events Following Immunization with Influenza Vaccines in Canada, 2012-15
N. Ahmadipour, C. Bancej, M. Gendron, J. Nkanza, R. Pless
Public Health Agency of Canada, Ottawa, Ontario, Canada

Objective: Review adverse events following immunization (AEFIs) reported to the Canadian Adverse Event Following Immunization Surveillance System (CAEFISS) in 2014-15 and compare these with the previous two influenza seasons.

Background: Annual influenza vaccination campaigns are implemented with a potentially different vaccine composition. The introduction of a different vaccine warrants enhanced surveillance for adverse events following immunization (AEFIs), defined as untoward or unexpected events which follow vaccination but which are not necessarily causally related.

Methods: All AEFI reports submitted to CAEFISS following an influenza vaccine administered between September 1st and March 31st for each of the three seasons were extracted. Each report underwent processing including MedDRA terminology coding and medical case review to assign a primary adverse event as main reason for reporting using Brighton collaboration' case definitions. AEFIs were analysed by age, gender, season, administered vaccine(s), main reason for reporting, and severity, presented as frequencies, proportions, and reporting rates per million doses distributed. Data cover nine provinces and three territories.

Results and Conclusion: In 2014-15, over 8 million vaccine doses were distributed among reporting jurisdictions. CAEFISS received 661 AEFI reports (reporting rate=63). Forty-two (6%) were serious, of which 39 were hospitalized and three were fatal outcomes unlikely related to vaccination. Females were predominant (73%), with mean age 39 years (median 41). The two most frequent reasons for reporting were vaccination site and allergic reactions among all age groups and both genders during all three seasons studied. This result was also consistent across vaccine brands except live attenuated influenza vaccine where localized rashes were reported along with allergic reactions. The reporting rate was less in 2014-15 compared to the previous two seasons. However, the severity level proportions were comparable across all three seasons. Age and gender distributions, severity level proportions and the pattern observed for main reason for reporting were similar across all seasons. The reporting rate was lower during 2014-15, suggesting lower reporting during this season. No safety concern was observed; nevertheless, close monitoring of influenza AEFIs during each season and feed-forward to global vaccinovigilance networks remain crucial components of post-market surveillance.

References:

Assessing the Feasibility of Monitoring Influenza Vaccine Safety in Pregnant Women Using Text Messaging
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Objective: Discuss the feasibility of using text messaging for vaccine adverse event surveillance in pregnant women.

Background: Inactivated influenza vaccine (IIV) is recommended for all pregnant women. Monitoring IIV safety, including in pregnant women, is an important part of both seasonal vaccine programs and pandemic influenza plans. Although no evidence suggests that IIV is associated with increased risk for adverse events in pregnant women vaccinated later in pregnancy, data are limited for women vaccinated in the first trimester. Most post-licensure vaccine studies do not capture non-medically attended events that may be clinically important and could affect future vaccination decisions. Of US adults, 90% have a cell phone. Text messaging programs can rapidly collect individualized data on both medically-attended and non-attended events. While we successfully demonstrated the use of text messaging for vaccine adverse event reporting in children, and others have demonstrated its use as a one-time query post-vaccination in pregnant women, the feasibility of its use to monitor post-vaccine events throughout pregnancy has yet to be studied.

Methods: The objective of this study was to assess the feasibility and accuracy of using text messaging to assess health status of pregnant women post-influenza vaccination through the end of pregnancy. We conducted a prospective observational study, in four practices in New York City, of pregnant women with a gestational age (GA) < 20 weeks at time of IIV vaccination who had a cell phone with text messaging; women with high risk pregnancies were not excluded. Most (80.2%, n=166) eligible women enrolled; 97.1% screened had text messaging. Messages were sent on: 1) days 0-2 (vaccination day and the next 2 days) assessing post-vaccination fever, 2) days 7, 14, 28, 42 assessing short-term events in the mother, and 3) from day 70 through participant-reported pregnancy end (monthly, then biweekly, then weekly). Messages included both fixed-choice (presence of vaginal bleeding, contractions, and/or fever) and open-ended responses. Final messages assessed pregnancy and neonatal outcomes, if applicable. Visit information was abstracted from electronic medical records (EMR), and study satisfaction assessed via an exit survey. Outcomes included response rates, d0-2 fever (T≥100.4F; 38C), reported pregnancy-related events and birth/neonatal outcomes.

Results and Conclusion: Median age was 32 years +/-6.2, GA at enrollment was 8.9 weeks +/-3.9; 57.8% were Latino, 33.1% Spanish-speaking, 21.7% publicly-insured and 27.1% uninsured at enrollment. 90.4% had unlimited text messaging plans. D0-2 text message response rates were high (89.7%-95.2%); one participant reported a d0-2 fever. D7-42 response rates ranged from 83.0%-89.1% with 11 unique text message reports of vaginal bleeding (eight of which were also in the EMR); four of contractions (all also in EMR). D70-259 response rates remained high (80.0%-91.7%). There were six unique reports of vaginal bleeding (three also in EMR); 25 of contractions (13 also in EMR). There were seven other unique pregnancy-related events, most commonly hypertension and diabetes; all also in EMR. Most (84.9%;n=141) completed the study (131 reported delivery, 10 reported no longer pregnant). Two fetal losses were not in the EMR, no additional losses were identified in the EMR. Of the 131 births reported, 86.2% had an EMR note confirming delivery. Most (96.9%) reported GA (30-42 weeks) including eight premature births (all confirmed in EMR). All reported a birthweight (1505–4545 grams). There were two other premature births in the EMR for women that had stopped texting. Ten reported neonatal problems, most commonly jaundice (nine confirmed in EMR). Nearly all (94.6%) would take part in a future text message study; 14.2% reported taking part affected how they felt about vaccine safety, all positively.
In addition to determining feasibility of text messaging, our study showed no unexpected adverse events among the pregnant women. Given the high response and retention rates, this study demonstrated the feasibility of text messaging for active vaccine safety surveillance sustained throughout pregnancy.

References:


An Efficient Method for Vaccine Safety Surveillance

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Objective: Identify an efficient method of studying vaccine safety that can be applied to resource poor areas.

Background: Ongoing surveillance to assess and monitor vaccine safety is critical worldwide. Methods must be practical and efficient in order to monitor numerous vaccine-adverse event pairs.

Methods: We summarized immunization data on our health population by age, gender and dates of all vaccines. We used this summarized data to calculate expected vaccine exposures in case centered studies. Risk sets consisting of cases and all matched controls are constructed from the summarized immunization data on the entire population, with matching on age, sex, and the same vaccine in the 9 months prior to the onset of the case. We applied a case-centered logistic regression model to estimate the Odds ratios (ORs) of vaccination within the exposure interval vs. the comparison interval, with confidence intervals and p-values. The method uses only vaccinated people in the analysis, thus controlling for differences in vaccinated vs. unvaccinated individuals. By anchoring to the date of onset, it also controls for time-varying confounding, such as seasonality. We applied this method for Erythema multiforme following vaccines of any kind, using automated data from 2007-12.

Results and Conclusion: Odds ratio (OR) of any vaccine and subsequent EM was 0.88 (95%CI 0.35-1.88). ORs for MMR, IPV, DTaP, and Hepatitis B were all zero. For PNCV7 and PNCV13, ORs were 1.36 (0.41-3.53) and 1.33 (0.06-7.92) respectively. ORs, 95% CIs, and p-values were calculated for all vaccines. We demonstrated the utility of this approach using summarized, automated data. The approach could be tailored to any population with known age and vaccine dates. Cases must be found, confirmed, and their immunization dates recorded, but a random sample of cases, and using weekly (or possibly monthly) rates with age groupings would suffice. This method could be considered in areas of limited resources, as long as rates of immunization by age and week are recorded.

References:


Cases of Postural Orthostatic Tachycardia Syndrome (POTS) Reported to the Vaccine Adverse Event Reporting System (VAERS) Following Human Papillomavirus (HPV) Vaccination, June 1, 2006 – September 1, 2015

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Objective: Describe the frequency and cases of Postural Orthostatic Tachycardia Syndrome (POTS) reported to the Vaccine Adverse Event Reporting System (VAERS) following Human Papillomavirus (HPV) vaccination.

Background: Since June 2006, three HPV vaccines have been licensed in the United States: Bivalent HPV vaccine [2vHPV], HPV Quadrivalent vaccine [4vHPV], and HPV 9-valent vaccine [9vHPV] for prevention of cervical and other cancers caused by HPV infection. Over 249 million doses have been distributed worldwide, including over 81 million in the US. Cases of postural orthostatic tachycardia syndrome (POTS) have been reported in the literature after HPV vaccination. A recent review by the European Medicines Agency found no causal relationship between HPV vaccine and POTS. We characterized reports of POTS following HPV vaccination submitted to the Vaccine Adverse Event Reporting System (VAERS), a US passive surveillance system.

Methods: We searched VAERS for all reports of POTS after any HPV vaccine received between June 1, 2006 and September 1, 2015. We used the terms “postural orthostatic tachycardia syndrome”, “dizziness postural”, and “postural reflex impairment” from the Medical Dictionary for Regulatory Activities (MedDRA) as search criteria. POTS was defined as: (1) heart rate increment of ≥30 beats/min within 10 minutes of standing or head-up tilt in the absence of orthostatic hypotension, (2) symptoms worsening with standing and improving with recumbence, (3) symptoms lasting ≥6 months, and (4) absence of other overt cause of orthostatic symptoms or tachycardia. Clinicians reviewed all reports of POTS and available medical records to confirm the diagnosis.

Results and Conclusion: VAERS received 49,519 reports during the pre-specified time period following HPV vaccination; 160 (0.4%) reports met the search criteria and 38 (0.008%) met case definition criteria for POTS. Nineteen of 38 confirmed cases (50%) were reported from the US, while the remaining 19 were reported from foreign countries (Denmark and Japan). The median interval between vaccination and symptom onset was 49 days. Of the 38 cases, 36 (95%) occurred after 4vHPV, 2 (5%) occurred after 2vHPV, and none occurred after 9vHPV. Fourteen cases (37%) had pre-existing conditions including asthma, chronic fatigue, hypothyroidism, and epilepsy. Review of VAERS reports following HPV vaccination identified few cases of POTS. Among US reports, we identified less than one confirmed case of POTS per million doses of HPV vaccine distributed. Pre-existing conditions in a sizable proportion of subjects with confirmed cases may confound determination of etiology of POTS symptoms.

References:

A Post-Licensure Observational Study to Assess the Safety of a Meningococcal Conjugate Vaccine in Subjects 11-21 Years of Age

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Objective: Discuss the safety profile of MenACWY-CRM vaccine in the general population of those aged 11-21 years.

Background: Meningococcal disease is a serious and potentially life-threatening infection caused by the bacterium Neisseria meningitidis. The Advisory Committee on Immunization Practices (ACIP) currently recommends routine administration of a meningococcal quadrivalent vaccine for all persons aged 11 through 18 years of age and certain young adults at increased risk of invasive meningococcal infection. MenACWY-CRM, a quadrivalent meningococcal conjugate vaccine, was approved by the US Food and Drug Administration for use in subjects aged 2 months to 55 years. This study was conducted as a post-licensure commitment between the manufacturer and the FDA to expand the knowledge of the safety profile of MenACWY-CRM vaccine in the general population of those aged 11-21 years.

Methods: This study was an observational study conducted at Kaiser Permanente Southern California (KPSC), a large health maintenance organization (HMO). The vaccination period included in the analysis was from September 30th, 2011 through June 30th, 2013. Twenty-six pre-specified events of interest (EOIs), including neurological disorders, autoimmune disorders, vasculitic disorders, hypersensitivity events, meningococcal disease, and suicide attempt, were identified in the electronic medical records for up to one year following vaccination. Specific risk windows were defined for each EOI, and the comparison window for all events started at the end of the risk window. EOI-specific algorithms were developed for automated identification of new onset cases. For a subgroup of pre-determined EOIs, medical records of subjects identified as potential cases using the algorithm were additionally reviewed by an independent case review committee (CRC) that was masked to vaccination status. For non-CRC reviewed EOIs, medical records of potential cases underwent further review by a physician co-investigator only if safety signals were detected. The self-controlled case series (SCCS) method was used to determine the relative incidence (RI) with 95% confidence interval (CI) for each EOI adjusted for seasonality. Stratified analyses were performed by age, gender, booster dose, and concomitant vaccination.

Results and Conclusion: A total of 48,899 vaccinated subjects with at least 6 months of HMO membership prior to vaccination were included in the analysis population. There were a total of 1,127 new onset EOI cases identified for analyses. Of these, 260 cases occurred in the risk windows and 867 occurred in the comparison windows. Statistically significant increased RIs were found initially for three non-CRC reviewed EOIs, namely seizure (RI: 2.9, 95% CI: 1.5-5.9), iridocyclitis (uveitis) (RI: 3.1, 95% CI: 1.1-8.7), and Hashimoto’s disease (RI: 5.5, 95% CI: 2.3-13.3). Following physician investigator chart review, the increased risk was no longer observed in the final analysis due to refutation of diagnosis, revision of date of onset, or identification of causes other than vaccination. The RI for Bell’s palsy, a CRC-reviewed EOI, was statistically significant (RI: 2.9, 95% CI: 1.1-7.5; 8 cases in the 84-day risk window and 10 cases in the comparison window). Stratified analyses demonstrated an increased risk for Bell’s palsy in subjects receiving concomitant vaccines (RI: 5.0, 95% CI: 1.4-17.8), and no increased risk for those without concomitant vaccine (RI=1.1, 95% CI: 0.2-5.5). All Bell’s palsy cases resolved completely within a short period of time. No increased risks were observed for the other EOIs. Among the 26 EOIs, an increased risk was found for the single EOI of Bell’s palsy, a form of facial paresis, following MenACWY-CRM vaccination. Stratified analysis showed that the increase was observed for those receiving concomitant vaccine(s). Facial paresis is listed as a potential adverse event in the US product package insert. The association between MenACWY-CRM given concomitantly with other vaccines and Bell’s palsy needs further investigation.
Generation of Inactivated Influenza Virus Vaccines Using Low-Energy Electron Irradiation

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Objective: Discuss how the use of low-energy-electro-irradiation (LEEI) can generate inactivated virus vaccines.

Background: Inactivated virus vaccines (IVVs) are usually produced by incubating pathogens with toxic chemicals such as formaldehyde or beta-propiolactone. This chemical treatment is very time consuming, and the inactivation efficiency displays a high variability. After the treatment the chemicals have to be removed to avoid toxic effects in the patient, leading to extensive downstream processing. Moreover, application of chemicals alters the virus structure, resulting in reduced neutralizing antibody specificity and therefore stimulates a weaker immune response. Ionizing radiation is a well-known alternative method for sterilization and inactivation of pathogens. Among the different types of ionizing radiation low-energy electron irradiation (LEEI) has until now not been used for vaccine production, although it has several advantages compared to other methods, e.g., lower emission of X-rays than γ-radiation or high-energy electron beam treatment; no heat generation during inactivation, resulting in a better conservation of the antigens, and enhanced reproducibility.

Methods: Using LEEI we generated inactivated Influenza viruses that almost completely maintain their immunogenic potential. We tested H3N8 (A/Equine2/Miami/1963) as a model virus for infectivity in cell culture based assays before and after LEEI treatment. In order to investigate the integrity of the surface proteins we analyzed electronic beam inactivated samples in ELISA- and HA-assays. Furthermore, we conducted animal immunization experiments to evaluate the immunogenic potential of the inactivated material. Since the inactivated material is sterile and can be used directly for vaccination, the irradiated material was mixed in a 1:1 ratio with adjuvant and injected twice into Balb/c mice in a 4 week interval. Antibody response was tested using ELISA-assays and virus neutralization tests.

Results and Conclusion: We reproducibly measure conservation of viral antigens around 80% in ELISA-assays compared to the untreated virus after inactivation. Using PCR- and electrophorese based methods we further demonstrate that mainly the nucleic acid of the pathogen is affected by LEEI. We observed a strong fragmentation of the nucleic acid, even with low doses, correlating with loss of infectivity. Animal immunization experiments revealed that the Influenza IVV material elicits strong immune responses and virus neutralizing antibodies. The obtained results might be transferrable to other influenza-strains and RNA-viruses as well. Inactivation with low energy electron beam provides a powerful and versatile method for a fast and reproducible inactivation of different classes of pathogens.

References:
What Is Pneu with Pneumococcal Disease in Children in the Conjugate Vaccine Era
S. L. Deeks, J. Fediurek, J. B. Gubbay, M. Policarpio, S. Wilson, K. Wong
Public Health Ontario, Toronto, Ontario, Canada

Objective: Explain why serotype-specific incidence of pneumococcal disease is important to document in order to determine pneumococcal conjugate vaccine program impact.

Background: A publicly-funded childhood pneumococcal vaccination program has been in place in Ontario, Canada (population approximately 13.5 million) since 2004. Initially, a 7-valent pneumococcal conjugate vaccine (PCV7) was introduced, followed by a 10 valent (PCV10) in October 2009, and finally a 13-valent (PCV13) in November 2010. PCV13 is given at 2-, 4- and 12 months of age. We reviewed invasive pneumococcal disease (IPD) incidence in Ontario children to assess serotype (ST) distribution, with a focus on ST 3 as there has been some suggestion of lower vaccine efficacy for this ST.

Methods: We extracted confirmed cases of IPD occurring in Ontario between January 2005 and December 2014 from the integrated Public Health Information System (iPHIS) and analyzed using SAS v9.3 and Microsoft Excel 2010. Cases from 2007 onwards (date when reliable serotyping data retention began) were classified according to ST including those covered by PCV7 and unique PCV13 ST excluding ST 3. We also examined temporal trends in ST 3 and in non-vaccine serotypes (NVSTs). Serotyping was performed by the capsular swelling (Quellung) reaction. We focused the ST analysis on children < 5 years. We used Poisson regression to assess trends over time and considered a p value of < 0.05 as significant.

Results and Conclusion: Over the 10 year period the annual IPD incidence was relatively stable ranging from 7.4 to 9.7 per 100,000 population. Adults 65+ years had the highest age-specific incidence throughout the period followed by children < 1 and 1-4 years. Among all children < 5 years, during the PCV7 era (2005-09) the incidence fluctuated from 11.2 to 20.5 per 100,000 population, with a significant increase over the period. Since PCV13 introduction incidence has significantly decreased to a low of 10.0 per 100,000 population < 5 years in 2014.

ST-specific analysis among children < 5 years revealed a significant decrease in incidence of STs covered by PCV7 since 2007. Among STs unique to PCV13 (excluding ST 3) there was a significant increase between 2007 and 2010 followed by a significant decrease between 2010 and 2014. ST 3 incidence remained stable throughout including in the PCV13 era. In contrast, there was a small non-significant increase in NVSTs between 2007 and 2014.

Although IPD remains burdensome in Ontario, our analysis revealed that the overall incidence among children < 5 years has decreased since PCV13 introduction suggesting vaccine program impact. ST-specific analysis revealed that the incidence of ST 3 remained stable suggesting that vaccine effectiveness for ST 3 may be lower than that of other serotypes covered by PCV13.

References:

Those Who Cannot Remember the Past Are Condemned to Repeat It (Santayana).
Growing up Before Vaccines
E. F. Boudreau1, C. H. Hoke, Jr.2
1Children of Uganda, Columbia, MD; 2Self Employed, Columbia, MD

Objective: Compare life growing up before and after the introductions of available vaccines.

Background: In recent years, vaccines have contributed to astounding successes in prevention of many infectious diseases that were formerly epidemic. Yet on occasion, some parents resist having their children immunized. From time to time, a review of the effects of epidemic infectious diseases on typical lives may remind us of how much less pleasant life would be without vaccines.
**Methods:** We reviewed existing vaccines approved for use by the US Food and Drug administration by participating in a Centers for Disease Control course on the clinical use of these vaccines. Separately, we sought specific anecdotes from our own clinical experience or from people who had been affected by the diseases that vaccines prevent. We reviewed the clinical manifestations, pathogenesis, and short and long term impacts of these diseases on the lives of affected individuals.

**Results and Conclusion:** All of the anecdotes we collected were touching, and some were very moving. In some cases, minor illnesses resolved (chickenpox, hepatitis A, adenovirus respiratory infections, rotavirus, pneumococcus, measles, mumps). In others, immediate death resulted (diphtheria, Japanese encephalitis, rabies, influenza). Some illnesses were severe, sometimes requiring long-term hospitalization and intensive care for recovery (tetanus, rabies, smallpox, pertussis) For some, we learned of severe long-term disabilities, resulting in catastrophic lifelong impact on affected individuals or their families (polio, Haemophilus influenzae type b, Congenital rubella, Japanese encephalitis, meningococcal meningitis). Some illnesses had long-term sequellae (liver cancer due to hepatitis B, cervical cancer due to human papilloma virus, shingles due to herpes zoster). We realize that in this era when one disease (smallpox) has been eradicated and others have been reduced to very low levels, the immediate urgency of immunizing children in accord with recommendations may not be obvious, even to physicians seeking nominations to run for president of the United States. We were struck by the potential seriousness of vaccine preventable diseases and by the realization that the risk of infection by these diseases is lifelong and worldwide.

**Reference:**

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**Decline of Maternal Measles Antibodies in Infants in Tianjin, China**

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**Objective:** Describe concordance of measles immunity between mothers and their infants.

**Background:** Measles continues to be a major cause globally of childhood morbidity and mortality and was responsible for 145,700 deaths worldwide in 2013. Many countries have adopted measles elimination targets including China, which was originally slated for elimination in 2012 as part of the WHO’s Western Pacific Region measles control plan. China’s elimination goal was not met despite intensive control efforts over several years, and sustained levels of transmission continue to characterize measles epidemiology there. In order to better understand measles susceptibility in Tianjin, China, the University Of Michigan School Of Public Health and the Tianjin Centers for Diseases Control collaborated on a large, population-based, cross-sectional, seroprevalence study conducted throughout the municipality. The study included a special focus on documenting the serostatus of mother-infants pairs since infants appear to play a major role in ongoing disease transmission in China even though measles vaccination is provided free at age 8 months.

**Methods:** We interviewed and drew dried blood spots (DBS) from a systematic random sample of 2818 adults and children from every Tianjin district, including 809 mother/infant pairs. The DBS were tested for measles IgG to determine measles susceptibility.

**Results and Conclusion:** While the majority of mothers (81.5%) tested IgG positive, only 16.3% of all infants less than 8 months of age tested IgG positive. Among infants one month of age or less, only 40.3% were IgG positive. The IgG positivity decreased to 12.3% at age 3 months, 6% at age 5 months; no infants were IgG positive by age 7 months. There was no significant difference in in the percentage of infants with a measles positive IgG result by birthweight, rural vs urban district, or mother’s vaccination status, education and age group. Infants of mother’s with a history of measles infection and infants of mothers who are non-residents had a higher percentage of measles IgG positivity. Although waning maternal measles antibodies in infants is well-documented, we found this may be occurring at younger ages than previously thought. More rapidly waning maternal measles antibodies could have major implications for measles elimination programs in China and globally. New strategies to target measles transmission in this younger infant age group should be considered.
Objective: Explain the use of the 4 Pillars™ Immunization Toolkit to raise immunization rates.

Background: Adult vaccination rates fall short of national goals, reinforcing the need to increase vaccination efforts in primary care. The 4 Pillars™ Immunization Toolkit, an evidence-based, step-by-step guide for making patient- provider- and system-oriented changes to improve adult vaccination, was implemented in primary care practices to increase adult influenza and Tdap vaccination rates.

Methods: 25 primary care practices were selected in Pittsburgh and Houston, and stratified by city, location (rural, urban and suburban), and type (family or internal medicine) and randomized to the Year 1 (2013-14) intervention (Group 1 n=10, Group 4 n=3) or the Year 2 (2014-15) intervention (Group 2 n=9, Group 5 n=12) group. The four sites continued in the active intervention in Year 2 (Group 3). The 4 Pillars™ Immunization Toolkit uses strategies based on the Task Force on Community Preventive Services and includes: Pillar 1-convenient vaccination services; Pillar 2-patient notification of the availability and importance of vaccination; Pillar 3-improved office systems to deliver vaccines; and Pillar 4-motivation through an immunization champion. The toolkit and practice improvement options were presented at an all-staff meeting at each practice. A practice-based Immunization Champion worked with the researchers to implement toolkit strategies and received feedback on vaccines administered. Goals were set at a 20-25% increase over the number of vaccines given the year before intervention. Demographic and vaccination data were derived from de-identified EMR extractions for patients ≥18 years.

Results and Conclusion: Over the 2-year study, a cohort of 70,549 adult patients was followed; 35% were men, 56% were non-white and 35% were Hispanic and the mean age at baseline was 55 years. Baseline individual practice Tdap vaccination rates varied from 4% to 59% and after the intervention from 7% to 80%, with percentage point (PP) changes varying from 3 to 25. Average Group cumulative Tdap vaccination increased variably from a 7 PP change from 22% to 29% in the Year 1 intervention sites (P < 0.001 annually) up to a 19 PP change from 48% to 67% in the 2-year intervention sites (P < 0.001 annually). Baseline individual practice influenza vaccination rates ranged from a low of 23.6% to a high of 61.2% Over two years, 3 of 6 sites in Group 1 significantly increased influenza rates with an average increase of 5.1 percentage points (P < 0.001); 6 of 8 sites in Group 2 significantly increased rates with an average increase of 6.0 PP (P < 0.001); 3 of 4 sites in Group 3 significantly increased influenza vaccination with an average increase of 9.6 PP (P < 0.001); all 6 of the sites in Groups 4 and 5 significantly increased rates with an average increase of 3.4 PP and 8.6 PP, respectively (P < 0.001). The 4 Pillars™ Immunization Toolkit appears to increase adult immunization rates within primary care practices over 2 years.

References:
S18
Viral Quasispecies Population Structure of Structural and Non-Structural Asibi/17D Chimeric Yellow Fever Virus
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Objective: Describe the use of reverse genetics to study attenuating mutations in live attenuated yellow fever 17D vaccine.

Background: Serial passage of wild-type Asibi strain 176 times in mouse and chicken tissue yielded 17D, one of the most effective and safe live attenuated vaccines known to date. Despite the derivation of 17D over 75 years ago, the mechanism of attenuation is still poorly understood. This study utilized structural (prME) and non-structural (NS4B-95) infectious clone (IC)-derived Asibi/17D chimeric viruses to investigate the molecular basis of attenuation and elucidate the possible mechanism of attenuation. RNA viruses are known to exist as populations of virions of differing RNA sequence, known as quasispecies population. Quasispecies population structure can be investigated using next generation sequencing (NGS). It is hypothesized that attenuation of 17D is due to mutations in 17D that result in lack of quasispecies population contained in wild-type Asibi virus.

Methods: The genomes of unpassaged IC-derived Asibi/17D chimeric, IC-derived Asibi strain, and IC-derived 17D-204 vaccine strain viruses were sequenced using NGS and viral quasispecies population assessed by determining RNA subpopulations and Shannon’s entropy of nucleotide distributions within the genome.

Results and Conclusion: As hypothesized, IC-derived Asibi strain and IC-derived 17D-204 vaccine strain differed in viral quasispecies population structure. Significantly, Shannon entropy for both prME and NS4B-95 Asibi/17D chimeric viruses differed in genes other than the targeted region when compared to the respective backbone viruses. Introduction of prME or NS4B-95 mutation into the Asibi and 17D backbone yielded no detectable RNA subpopulation with our methods used, and the Asibi chimeric viruses differed from IC-derived Asibi strain virus which possesses an RNA subpopulation with typical wild-type diversity.

References:

S19
RSV Assay Strengthening Work to Advance Vaccine Development
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Objective: Describe the current ability to assess immunogenicity and compare results across diverse respiratory syncytial virus (RSV) neutralizing assay formats used to support vaccine development and ongoing assay improvement efforts.

Background: The wide variety of neutralization assay formats used globally is a barrier to the standardized evaluation of different RSV vaccine candidates. The classical plaque reduction neutralization test is a labor-intensive and relatively low-throughput assay format. While microneutralization assay formats have many components in common with the plaque reduction neutralization test, are generally higher throughput, and often utilize automated methods to read out results, microneutralization assay protocols vary widely. Furthermore, assay parameters like cell lines, virus stocks, and complement use are not consistent among assays. To inform assay strengthening needs, the purpose of this study was to survey across a diverse array of assay formats that quantitate RSV neutralizing antibodies.

Methods: Using a common sample panel for testing, the degree of overall agreement among output from existing assays was evaluated to inform the need for assay standardization and potential of an IS to improve...
The harmonization of assay results. A total of 13 laboratories participated in the blinded survey by testing a sample panel comprised of 57 samples chosen to span the reportable range of the assays. Each laboratory performed the assay using its existing protocol, analyzed the resulting data using its current methodology, and reported assay results to PATH as final valid neutralizing antibody titer values using a standardized form. An independent statistical analysis was conducted to measure overall agreement between-laboratory and between-sample variances. A harmonization exercise was also performed using selected specimen types from the panel as mock internal standards to inform whether the use of a standard might improve the level of agreement.

**Results and Conclusion:** Statistical analysis showed that accuracy (agreement of the laboratories on the titer of each sample) varied widely among the assays while precision (closeness of the titer results for the samples) was consistently high. Furthermore, harmonization attempts using selected samples as mock standards significantly improved agreement across diverse neutralizing antibody assay formats. These observations strongly suggest that establishing an IS may improve output agreement across assay formats. Additionally, the within-sample and within-laboratory variability results showed that samples with comparably low variability in multiple assay types and formats that may be useful for developing an IS could be identified.

**References:**

**S20**

**A Replication Defective Human Cytomegalovirus (CMV) Vaccine**

T. Fu

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**Objectives:** Explain the importance of CMV as a vaccine target. Discuss recent progress on effective CMV vaccine design and a promising candidate currently under clinical evaluation.

**Background:** Congenital CMV infection is one of the leading causes of birth defects; developing a prophylactic vaccine is an unmet need for public health. Naturally acquired CMV immunity in women prior to conception is effective in preventing CMV transmission to fetus during pregnancy; both humoral and cellular immunity to CMV are likely playing a role in blocking the transmission. However, a live attenuate CMV vaccine is difficult to develop since the CMV is known to establish persistent and life-long infection in host.

**Methods:** To develop a safe CMV vaccine incapable of establishing productive and persistent infection, we first restored expression of viral gH/gL/pUL128-131 pentameric gH complex, and then applied a genetic/chemical switch to two viral proteins essential for replication. This design would allow regulation of viral replication with a small synthetic molecule; the vaccine virus cannot replicate without the chemical in culture.

**Results and Conclusion:** The vaccine was immunogenic in mice and rabbits, mostly due to the restored pentameric gH complex. It was also effective in induction of durable neutralizing Abs, in rhesus monkeys. Furthermore, it can induce balanced CD4 and CD8 T-cell responses. The vaccine was extensively evaluated for its virological properties. The vaccine is currently under Phase I evaluation.

**References:**
RSV Infection & Vaccines: Antigenic Fingerprinting Following RSV Vaccination and Infection Identify Novel Vaccine Targets
S. Fuentes, H. Golding, S. Khurana
US Food and Drug Administration, Silver Spring, MD

Objective: Identify the need for comprehensive analysis of antibody immune response using unbiased technologies following vaccination vs. infection in humans.

Background: Respiratory syncytial virus (RSV) is the most important cause of viral lower respiratory tract illness (LRI) in infants and frail elderly worldwide. Since serious RSV disease can occur in high-risk individuals, who have experienced previous RSV infection, as well as in RSV-naïve infants, there has been concerted effort in the past decade to develop RSV vaccine based on new technologies including VLPs and proteins. Several vaccine candidates are already in clinical trials. In parallel with the intensive vaccine development efforts, there is an urgent need to improve the analytical tools available for studying immune responses elicited by different vaccine platforms and the impact of different adjuvants on antibody mediated neutralization of Gp A and Gp B viruses. It is also important to identify the most important attributes of RSV vaccines including epitope repertoires and antibody affinity maturation that are likely to correlate with in vivo protection.

Methods: To address this need, we generated Whole-Genome Fragment-Phage-Display-Libraries (GFPDL) of RSV to probe the humoral immune responses following RSV infection and vaccination. We have constructed GFPDL expressing RSV gene-fragments encompassing of the ‘F’ and ‘G’ surface protein genes ranging between 15-100 aa as fusion proteins with the bacteriophage pIII coat protein. These RSV-libraries were used to analyze convalescent sera from individuals exposed to RSV, and for mapping the epitopes of neutralizing monoclonal antibodies. We have also developed a simple, fast, high-throughput reporter-gene based RSV microneutralization assay to measure neutralization efficacy of vaccine or infection induced monoclonal and polyclonal antibodies. Additionally, we produced properly folded RSV-G, pre-fusion and post-fusion form of F viral proteins, known to be targeted by protective antibodies, for use with Surface Plasmon Resonance (SPR) based real time kinetics assay to measure antibody affinity of monoclonal antibodies and human polyclonal sera following RSV vaccination or infection.

Results and Conclusion: These novel tools were used for elucidation of RSV-specific antibody repertoire following vaccination vs. infection (including breadth, targeted epitopes, isotypes, and affinity). Importantly, several novel epitopes were identified in pre-fusion F and an immunodominant epitope in G. These studies identified unlinked evolution of anti-F and anti-G responses and supportive evidence for immune pressure driven evolution of RSV-G. These findings could help development of new RSV serodiagnostic and develop knowledge based effective countermeasures including vaccines.

References:
**Enhanced H7N9 Vaccine Immunogenicity Engineered by Regulatory T Cell Epitope Deletion in Hemagglutinin**

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**Objective:** Illustrate a bioinformatic- and structure-guided approach to design of more effective vaccines.

**Background:** H7N9 influenza hemagglutinin (HA) elicits weak neutralizing antibody responses in natural infection and vaccination. Limited helper T cell response could explain the poor immunogenicity observed. We hypothesize a T cell epitope in H7-HA stimulates regulatory T cells (Tregs) capable of suppressing crucial signals needed for protective antibody production. Furthermore, deletion of the epitope without perturbing neutralizing B cell epitope structures may increase H7-HA immunogenicity to produce an optimized vaccine.

**Methods:** Immunoinformatics tools were used to identify H7N9 class II HLA epitopes with high potential to cross-react with Tregs educated on human antigens. Phenotypes of T cells responding to predicted epitopes were assessed by immunostaining and flow cytometry and function by ELISpot assay. Humoral immunogenicity of epitope-modified H7-HA was determined in humanized mouse immunizations.

**Results and Conclusion:** In peripheral blood leukocyte cultures, H7N9 epitopes with significant human homology expanded CD4+CD25+FoxP3+CD39+ Tregs and reduced IFNγ secretion when co-incubated with other H7N9 epitopes with low potential cross-reactivity. We applied this finding to design an antigenically improved H7-HA by introducing three modifications to recombinant HA (rHA) that delete a highly conserved Treg activating epitope. Engineered rHA (Opt1 rH7-HA) demonstrated both preserved antigenicity and improved immunogenicity in humanized mice. Monoclonal antibodies raised against wild type H7-HA recognized Opt1 rH7-HA with affinity equivalent to the wild type protein, suggesting that modifications did not induce significant structural perturbations. Similarly, human polyclonal sera demonstrated identical binding profiles against Opt1 and wild type rH7-HA. Vaccination of immunodeficient sera reconstituted with human PBMCs (N=8) using non-adjuvanted Opt1 rH7-HA stimulated higher anti-H7-HA IgG titers and higher frequencies of anti-H7-HA plasma cells than mice immunized with wild-type protein. In a related study, HLA-DR3 transgenic mice were immunized with Alum-formulated H7N9 virus-like particles containing either Opt1 or wild-type H7-HA and hemagglutinin inhibition (HAI) titers were measured. Opt1 rH7-HA stimulated protective levels of HAI antibodies suggesting that modifications of H7-HA preserved neutralizing epitopes. The Opt1 H7N9 VLP vaccine raised HAI antibodies sooner and at lower doses than wild-type vaccine.

Epitope-driven approaches to vaccine design that involve careful consideration of T cell subsets primed in immunization promise to enhance vaccine efficacy.

**References:**

**Background:** We have previously identified a CD1d-binding, iNKT cell-stimulatory glycolipid, called 7DW8-5. This compound is able to exert a strong adjuvant effect on the protective CD8+ T cell response of rodent malaria vaccines in a mouse model, as well as the CD8+ T cell immunogenicity of a human malaria vaccine in an NHP model. Recently, we have established humanized mice that mimic human immune system (HIS) cells, particularly human CD8+ T cells and invariant natural killer T (iNKT) cells. Therefore, in the present study we investigated whether 7DW8-5 exhibits an adjuvant effect on human immune responses, using our HIS mice.

**Methods:** HIS mice were generated by first transducing HLA-A2 along with human genes encoding CD1d, and selected human cytokines into immuno-deficient NSG mice, using adeno-associated virus (AAV)-mediated gene transfer. The human gene-transduced NSG mice were then exposed to sublethal irradiation. They were then immediately engrafted with HLA-matched human hematopoietic stem cells. More than 80% of white blood cells of the HIS mice were found to be human leukocytes, including human CD8+ T cells and iNKT cells. In order to determine whether 7DW8-5 can display an adjuvant effect in HIS mice, the HIS mice were first immunized with a human malaria vaccine with or without the glycolipid. Ten days later, PBMCs were collected and the level of malaria-specific human CD8+ T cell response was determined. In addition, the level of protective anti-malaria immunity was determined by challenging the HIS mice with live malaria parasites that express a human malaria antigen, twelve days after immunization.

**Results and Conclusion:** We found that co-administration of 7DW8-5 with the human malaria vaccine not only resulted in eliciting a strong malaria-specific human CD8+ T cell response, but more importantly it enhanced the protective human CD8+ T cell mediated immunity against malaria infection. The HIS mice generated in this study provide compelling evidence for a significant adjuvant effect of 7DW8-5 in the context of a human immune system, thereby allowing us to swiftly evaluate the immunogenicity and efficacy of various human adjuvant and vaccine candidates in a pre-clinical setting.

**References:**

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**S24**

**Comprehensive Mutagenesis of Dengue Virus Envelope Proteins to Map Antibody Epitopes and Functional Regions**

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Integral Molecular, Inc., Philadelphia, PA

**Objective:** Explain how, for the dengue Env protein, specific epitope residues critical for antibody binding can be rapidly determined using a high throughput analysis of comprehensively mutated Env protein.

**Background:** To characterize the extent and nature of the immune response to dengue virus (DENV) infection, we developed a high-throughput strategy, shotgun mutagenesis, that enables the identification of both linear and conformational epitopes in a fraction of the time required by conventional approaches. To enable epitope mapping for DENV envelope protein E (Env), we applied this strategy to DENV prM/E proteins from all four DENV serotypes.

**Methods:** For each DENV serotype, 1-4, we used shotgun mutagenesis to create comprehensive libraries of single point mutations in the DENV prM/E envelope proteins, in total 3,380 point mutations in DENV prM/E. Each library of individual mutant expression plasmids was arrayed in 384 well plates and transfected into human cells for native expression and folding. After transfection, libraries were screened using high throughput robotic assays to assay the immunoreactivity of MAbs to prM/E variants in each individual well of the library plates,
with binding quantified by high-throughput flow cytometry. In addition, we used a previously developed DENV reporter virus particle (RVP) system (Mattia et al., 2011) to produce DENV virions from the four DENV mutagenic libraries. This allowed us to screen each individual DENV Env variant protein for DENV particle budding by sandwich ELISA and for infectivity by expression of a luminescent reporter protein.

**Results and Conclusion:** We have mapped close to 300 MAb epitopes using the four DENV prM/E mutation libraries. In addition, we have identified Env variants that showed increased DENV virion budding, up to 5-fold above wild-type. For DENV3, analyses of budding and infectivity identified residues that are critical for virus infectivity, but that do not affect E protein expression, folding, virion assembly, or budding. We have demonstrated the ability to rapidly map epitopes, including quaternary epitopes across DENV prM/E. The correlation of specific epitope residues with their ability to protect against DENV has identified neutralizing epitopes and provided new targets for vaccine development. We were also able to identify critical residues throughout DENV prM/E that are required for infectivity and propose atomic-level models of how E protein mediates fusion.

**References:**

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**Identification of Aim2 as a Mediator for Alum’s Adjuvant Effects**

**Objective:** Discuss a previously unreported link between Alum–induced pyroptotic cell death and vaccine immunogenicity that is instrumental in shaping antigen-specific immune responses.

**Background:** Although Alum is a widely used vaccine adjuvant, the understanding of its immunostimulatory effects remains incomplete. Recent reports suggest that cellular DNA released by apoptotic process at the site of alum administration may play an important role in its adjuvant effects. In the current study, we investigated the role of the cytosolic DNA sensor, absent in melanoma 2 (Aim2) in shaping adaptive immune responses.

**Methods:** Inactivated influenza vaccine was used as the model antigen to study the hemagglutinin (HA)–specific antibody responses and anti-viral cytokines in the wild type B6x129 (Aim2+/+) mice and Aim2 KO (Aim2−/−) mice. Mice were immunized with influenza vaccine with or without Alum adjuvant at Weeks 0 and 2. Serum samples were collected prior to immunization and 2 weeks after each immunization to evaluate the HA-specific antibody responses by ELISA. Tissue biopsies of immunized mice were also taken at 6 and 24 hours post immunization for cytokine analysis by RT-PCR.

**Results and Conclusion:** The Aim2 inflammasome directs maturation of the pro-inflammatory cytokines IL-1β and IL-18 and an inflammatory form of cell death called pyroptosis. Antibody responses were significantly reduced in Aim2-deficient mice receiving the seasonal trivalent inactivated influenza vaccine adjuvanted with Alum. Surprisingly, Aim2-deficient mice also exhibited significantly lower levels of IFN-αβ at the site of injection. These results indicate a previously unreported link between Alum–induced pyroptotic cell death and vaccine immunogenicity that is instrumental in shaping antigen-specific immune responses.

**References:**
Aerosolized Ebola Vaccine Elicits Robust Antibody and Lung-Resident T cell Responses and Protects Non-Human Primates against Virus Challenge

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Objective: Discuss the development of a needle-free vaccine against Ebola virus, induction of the immune response to the vaccine, and protection against Ebola virus challenge.

Background: Studies with non-human primates suggest that aerosols of most biothreat agents, such as Ebola virus (EBOV) are infectious, and the virus can be transmitted through biological fluid droplets, fomites, and self-inoculation through contact. These observations suggest that respiratory tract mucosa may be an important portal of entry for EBOV and emphasizes the importance of immune protection of the respiratory tract. A noninvasive needle-free respiratory tract vaccine against EBOV will not require trained medical personnel making it useful for EBOV outbreaks. Aerosolized vaccination via the respiratory tract has never been tested for EBOV or other hemorrhagic fever viruses.

Methods: We examined the immunogenicity and protective efficacy of an aerosolized human parainfluenza virus type 3-vectorized vaccine expressing the glycoprotein (GP) of EBOV (HPIV3/EboGP) delivered to the respiratory tract.1 Rhesus macaques were vaccinated with aerosolized or liquid HPIV3/EboGP or an unrelated, intramuscular, Venezuelan equine encephalitis replicon (VRP) vaccine expressing EBOV GP.

Results and Conclusion: High EBOV-specific IgG, IgA and neutralizing antibody titers were detected in serum and respiratory tract mucosal samples from aerosolized HPIV3/EboGP recipients, which exceeded or equaled titers observed in liquid HPIV3/EboGP or VRP recipients. Multi-parameter flow cytometry analysis of CD8+ and CD4+ T cells isolated from PBMC, lungs and spleens of vaccinated macaques was performed. It demonstrated that the HPIV3/EboGP vaccine induced an EBOV-specific cellular response that was greatest in the lungs and yielded polyfunctional CD8+ T cells, their subset expressing CD103 (αE integrin) and predominantly type 1 CD4+ T helper cells; the magnitude of the CD4+ T cell response was greater in aerosol vaccinees. Moreover, aerosol vaccination induced a greater activation of CD8+ and CD4+ T cell populations in lungs than in blood and spleen, as evidenced by both the numbers of cytokines and other markers of activation expressed, and the levels of their expression. In contrast, vaccination with VRP induced T cell response predominantly in spleen. We also show that one aerosol HPIV3/EboGP dose conferred 100% protection to macaques exposed to EBOV by the IM route. These data provided the basis for advancing HPIV3/EboGP to a phase I clinical trials currently in progress. In addition, pre-clinical studies comparing HPIV3/EboGP with vaccine constructs based on alternative human and avian respiratory paramyxoviruses are also being performed.

Reference:


E. Coyle, S. Fuentes, S. Khurana, S. Ravichandran
US Food and Drug Administration, Silver Spring, MD

Objective: Define the role of antibody epitope repertoire diversity, antibody affinity maturation, and the importance of anti-GP antibody isotype class for EBOV neutralization and correlates of protection in vivo.

Background: Development of an effective vaccine against Ebola has been declared a high priority by public health authorities around the world. Three vaccine candidates are in clinical trials. The immune responses that are generated by different candidate Ebola vaccines (VSV, Ad vector, VLP +/-Adjuvant) are under investigation, but the correlates of protection against Ebola are not fully understood. Antibody response contributes significantly to the protection against EBOV infection, however there is limited knowledge on the quality of
the polyclonal antibody responses generated following vaccination with different vaccine platforms in terms of antibody epitope repertoires, antibody isotypes, and antibody affinity.

**Methods:** Therefore, in parallel with the intensive vaccine development efforts, there is an urgent need to develop unbiased molecular technologies for comprehensive analysis of immune responses elicited following EBOV infection and by different vaccine platforms. It is important to identify the most important attributes of Ebola vaccines including epitope repertoires, antibody isotype and affinity maturation. Such information could help in identifying new correlates of protection against homologous and heterologous EBOV strains. To address this need, we generated Whole-Genome Fragment-Phage-Display-Libraries (GFPDL) of different Ebola strains to probe the humoral immune responses following Ebola infection and vaccination.

**Results and Conclusion:** We constructed GFPDL with > 10E6 individual clones expressing Ebola gene-fragments encompassing the GP surface protein sequences ranging between 15-300 aa (of Zaire, Sudan and Bundibugyo). These Ebola phage display libraries are currently used to analyze post-vaccination sera, and for mapping the epitopes of neutralizing monoclonal antibodies. Additionally, we employed properly folded Ebola-GP viral proteins and domains from different Ebola strains, known to be targeted by protective antibodies, for use with Surface Plasmon Resonance (SPR) based real time kinetics assay. The SPR assays are being used to measure affinity of monoclonal antibodies and polyclonal serum/plasma antibodies from humans and NHP following Ebola vaccination or infection. These novel methodologies could be valuable tools for elucidation of Ebola-specific antibody repertoire and antibody quality following vaccination vs. infection. The identified new epitopes and protective targets could be used to develop cross-protective effective Ebola countermeasures including vaccines, therapeutics, and serodiagnostics

**References:**


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**Mapping Antibody Epitopes on the Ebola Virus Envelope Protein by Shotgun Mutagenesis**

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**Objective:** Explain how, for the Ebola virus surface GP protein, specific epitope residues critical for antibody binding can be rapidly determined using a high throughput analysis of comprehensively mutated GP.

**Background:** The Ebola virus (EBOV) glycoprotein (GP) plays an essential role in EBOV infectivity and is a target of the immune system, yet our understanding of the immune response to EBOV infection is hampered by the absence of complete information on epitopes on GP. To identify antibody binding sites on EBOV we applied our high throughput shotgun mutagenesis epitope mapping technique to EBOV GP.

**Methods:** We used shotgun mutagenesis to create a comprehensive library of single point mutations in the EBOV GP envelope protein. Alanine scanning mutagenesis was used to create 641 EBOV GP variants that were individually arrayed in 384 well plates. Mutations were then expressed in human cells and assayed for reactivity with a variety of monoclonal antibodies (MAbs), using high-throughput flow cytometry to identify the most energetically important GP residues required for the binding of each MAb.

**Results and Conclusion:** Cocktails of MAbs that target EBOV GP have shown great promise as anti-EBOV therapeutics and were used under emergency compassionate treatment protocols in the 2014 EBOV outbreak. However, the detailed epitope binding sites for the MAbs in ZMapp, and the related ZMAb and MB-003 cocktails, have not been fully elucidated. We first applied our EBOV mutation library to the ZMapp and related MAb cocktails and resolved the amino acid epitopes of all six MAbs in these cocktails, as well as the commonly used reference MAb KZ52.¹ We have also epitope mapped a number of additional MAbs that recognize EBOV GP, including MAbs obtained from a human survivor of infection by the Bundibugyo ebolavirus.² Identification of epitope residues for the ZMapp cocktail MAbs distinguishes between MAbs that bind competitively in the same
region of GP but using different epitope residues, helps explain their reactivity against different EBOV species, predict viral evasion against these MAbs, and design new cocktails of MAbs that may offer improved functional complementarity. The application of epitope mapping to these and additional anti-EBOV MAbs is already expanding our understanding of how the immune system recognizes EBOV GP. Correlation of these and future MAbs epitopes with their neutralizing capabilities will be invaluable in characterizing the immune response to EBOV and in developing anti-EBOV biologic or vaccine therapeutics.

References:

A Genome-Wide Association Study Identifies Major Loci Associated with Measles Vaccine-Specific Immune Responses
I. H. Haralambieva, R. B. Kennedy, B. R. Larrabee, I. G. Ovsyannikova, G. A. Poland, D. J. Schaid
Mayo Clinic, Rochester, MN

Objective: Discuss the first genome-wide association study (GWAS) with vaccine-induced immune measures in healthy subjects who received live measles virus vaccine

Background: We have previously described genetic polymorphisms in candidate immune response genes that are associated with inter-individual variations in humoral and cellular immune responses to measles vaccine. To expand upon our previous work, we performed a genome-wide association study (GWAS) to discover single-nucleotide polymorphisms (SNPs) associated with measles virus (MV)-specific neutralizing antibodies and IFNγ-ELISPOT responses.

Methods: Our study cohort is a large population-based sample of 2,845 healthy subjects (age, 11 to 41 years; 782 females and 2,063 males), consisting of 5 separate recruitment efforts. Of these subjects, 2,507 (88.1%) were Caucasian. The average age at enrollment was 21 years (interquartile range [IQR], 16-25). A GWAS using 6,244,546 observed and imputed SNP markers (Illumina) was performed in a combined cohort (n=2,845) to identify the major loci affecting the immune response to MV. Humoral responses were determined by MV-PRMN antibody assay. Cellular responses were assessed by IFNγ-ELISPOT. Associations between SNP genotypes and immune response measures were determined via linear regression.

Results and Conclusion: The most prominent associations that reached a genome-wide level of significance (< 5 x 10^-8) was found with eight intronic SNPs in the MV receptor gene, CD46, on chromosome 1 (range of p-values 1.47 x10^-9 - 2.24 x10^-8). A previously found association of the CD46 SNP rs2724384 with decreased MV-specific antibodies was replicated in this GWAS (p=2.25 x10^-9). Additional SNP associations with measles neutralizing antibodies were mapped to the interferon-induced protein 44-like (IFI44L) gene (range of p-values 3.36 x 10^-9 - 3.08 x 10^-8) and uncharacterized LOC101929385 RNA gene (range of p-values 1.92 x 10^-9 - 4.98 x 10^-8) on chromosome 1. Specifically, missense SNP rs273259 in the interferon-stimulated innate gene IFI44L was significantly associated with neutralizing antibody levels (p=9.65 x 10^-9). We also identified SNP associations with the smallest p-value in the class II HLA-DRB (p=2.05 x 10^-7) and signal transduction carbohydrate sulfotransferase-9 (CHST9, p=3.54 x 10^-8) genetic regions on chromosome 6 and 18, respectively, as being significantly associated with IFNγ-ELISPOT response variations after measles vaccine. Interestingly, genetic variants in the IFI44L (rs273259, p=9.65 x 10^-9) and CD46 (rs1318653, p=1.68 x 10^-8) genes found in our GWAS have been recently linked to the measles-mumps-rubella vaccine-related febrile seizures.

These findings demonstrate that polymorphisms in the CD46, IFI44L, CHST9, and class II HLA genomic regions are strongly associated with inter-individual variation in immune responses to measles vaccine and represent a validation of our previous work. Further fine-mapping and functional studies will illuminate the biological mechanisms behind these associations.
References:

Immunization of Rabbits with Epstein-Barr Virus (EBV) gH/gL and gB Recombinant Proteins Elicits Higher EBV-Neutralizing Antibody Titers Than Those Induced by EBV gp350
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Objective: Discuss the new potential vaccine targets for a prophylactic Epstein-Barr virus vaccine.
Background: Epstein-Barr virus (EBV) has been strongly implicated in the etiology of multiple lymphoid and epithelial cancers, infectious mononucleosis, and post-transplant lymphoproliferative disease. There is currently no licensed prophylactic vaccine for EBV. EBV gp350, which binds to CD21/CD35 to gain entry into B cells, has been considered a promising target for an EBV vaccine but failed to prevent infection in a phase II clinical trial. Thus, alternative or additional target antigens may be necessary for a successful prophylactic vaccine.
Methods: We investigated the ability of recombinant EBV gH/gL heterodimeric and EBV gB proteins, in comparison with EBV gp350, to induce antibodies that prevent EBV infection of B cells. This was based on the known ability of gH/gL and gB proteins to coordinate, mediate EBV fusion with the B cell endosomal membrane, as well as the epithelial cell plasma membrane, and thus entry into the cytosol. We utilized Chinese hamster ovary cells to express recombinant monomeric and tetrameric gp350, monomeric and trimeric gH/gL, and trimeric gB proteins. We immunized individual groups of rabbits (n=5) s.c. x 3, with these proteins in alum + CpG-ODN adjuvant.
Results and Conclusion: We demonstrate, using GFP-EBV infection of Raji human B cell lymphoma cells that each protein induces EBV-neutralizing serum antibody with gH/gL>>gB>gp350 IC50 serum titers. We also demonstrate that tetrameric gp350 and trimeric gH/gL elicit higher serum EBV-neutralizing titers than their monomeric counterparts. These data strongly suggest a role for testing trimeric EBV gH/gL and trimeric EBV gB proteins, in addition to tetrameric gp350 protein, in a future prophylactic vaccine to prevent EBV infection of B cells, and potentially epithelial cells as well.
Reference:

Multivalent PRINT® Nanoparticulate Pneumococcal Vaccines: Polysaccharide Protein Vaccines Stimulate Robust B and T Cell Immune Response
A. L. Galloway, M. R. Stone
Liquidia Technologies, Research Triangle Park, NC

Objective: Explain the use of PRINT® nanoparticles as a novel system to produce a Pneumococcal polysaccharide and protein vaccine that induce robust serotype specific anti PnPS 1, 4, 5, 6A, 14, 19A, and 23F, and OPK responses equivalent to PCV13.
Background: A nanoparticle vaccine consisting of pneumococcal polysaccharides (PnP) and protein antigens (toxoids, surface proteins) has the potential to confer broader and enhanced protective immunity (antibody/cellular) against IPD and carriage/colonization. In partnership with PATH, Liquidia is developing a next generation
multivalent nanoparticulate polysaccharide vaccine for *Streptococcus pneumoniae* based on PRINT® technology which can elicit antibody and cellular (IL-17) responses. For example, PRINT® nanoparticle multivalent vaccines which incorporate key capsular PnPs (1, 4, 5, 6A, 14, 19A, 23F) and pneumococcal carrier protein/ immunogen (mutant pneumolysin - PLD and pneumococcal surface protein A - PspA) has been developed. 

**Methods:** Mice and rabbits (n =6) were immunized subcutaneously or intramuscularly with defined serotype/protein PRINT® formulations (day 1/29/57). The IgG (PnPs/protein) response to PRINT® formulations was evaluated and calibrated against PCV13 using the WHO IgG ELISA protocol adapted for animal models. Functional responses to animal sera were evaluated by opsonophagocytic killing (OPK) assay. Spleens collected on day 70 were analyzed for IL-17 and IFN-γ release from splenocytes in response to antigen stimulation.

**Results and Conclusion:** Single and multivalent serotype nonadjuvanted PRINT® formulations elicited robust serotype-specific antiPnPs1, 4, 5, 6A, 14, 19A, 23F, and OPK responses equivalent to PCV13. PRINT® formulations also induced PLD and PspA IgG antibody responses on par with soluble PLD and PspA antigens. Significantly, PLD/PnPs1, 5, 14 PRINT® pneumonia particles generated IL-17 responses. Incorporation of *S. pneumoniae* protein and polysaccharide antigens in PRINT® formulations induces antibody and cellular immune responses (Th1 and Th17). The incorporation of structurally and chemically diverse antigens demonstrates the broad potential of the PRINT® platform for nanoparticle vaccine applications.

**References:**

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**Strong, But Age-Dependent, Protection Elicited by a 2nd Generation DNA/Modified Vaccinia Ankara Simian Immunodeficiency Virus Vaccine**

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**Objective:** Describe the preclinical efficacy of DNA/MVA-expressed VLP to protect against serial rectal SIV challenges. Discuss the strong effect of age on the protective efficacy of an immunodeficiency virus vaccine and how the form of antigen and immunization regimen can reduce the need for a co-expressed GM-CSF adjuvant.

**Background:** Here we analyze the protective efficacy of a 2nd generation SIVmac239 prototype of the GOVX-B11 DNA/modified vaccinia Ankara (MVA) HIV vaccine that is undergoing clinical development. For the 2nd generation vaccine, the DNA prime was mutated to enhance the production of non-infectious virus-like-particles by inactivating the active site of protease (a mutation that is present in the human vaccine) and the regimen used a 16 week rest, rather than an 8 week rest, between the last two immunizations.

**Methods:** Five to 15 year old Rhesus macaques were inoculated intramuscularly at weeks 0 and 8 with 3 mg of a SIVmac239 DNA vaccine either co-expressing, or not co-expressing granulocyte-macrophage colony-stimulating factor (GM-CSF) and boosted at weeks 16 and 32 with 1x10⁸ TCID 50 of a SIVmac239 MVA vaccine. Animals were challenged 6 months later with 12 weekly intra-rectal exposures to SIVsmE660.

**Results and Conclusion:** Over the first six rectal exposures to SIVsmE660, 5-10 year old TRIM5α permissive rhesus macaques had a two times higher reduction in per exposure risk of infection than 10-16 year old animals (81% as opposed to 40%); and, over the 12 challenges administered, a 10 times higher per exposure risk reduction (76% as opposed to 7%). Elicited immune responses suggested that Ab, and not T cells, had played the key role in delaying infection. Levels of Env-specific IgG and IgA in serum, the specific activity of Env-specific IgG
in rectal secretions and IgG- and IgA-producing ASC showed modest correlations with the number of challenges to infection. Consistent with the poorer protection in older animals, each of these protection-associated Ab responses was significantly lower in older than younger animals. In contrast to the 1st generation vaccine, where co-expression of GM-CSF had enhanced the avidity of Env-specific Ab responses and protection, the 2nd generation vaccine achieved high avidity Ab and good protective responses without the need for the GM-CSF adjuvant.

On the basis of these findings, the non-adjuvanted GOVX-B11 vaccine will undergo further clinical development using a 16-week rest between the final two MVA boosts. And, given the strong effect of age on protection, efficacy testing with GOVX-B11 will be limited to youths and young adults.

References:

Live Imaging Animal Model of RSV for Evaluation of Vaccines and Therapeutics
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¹US Food and Drug Administration, Silver Spring, MD; ²Emory University, Atlanta, GA

Objective: Evaluate the use of in vivo imaging in preclinical studies compared to traditional methods of studying RSV progression and vaccine/therapeutic efficacy in mice.

Background: Respiratory syncytial virus is a leading cause of respiratory tract infection in infants and the elderly. Currently, the only licensed product for treatment of severe RSV disease in infants is Palivizumab, an antibody targeting the F protein. There are no approved vaccines for RSV and several vaccine candidates are under clinical development. Current methods to determine the efficacy of new RSV vaccine candidates or therapeutics in an animal model require the sacrificing of animal and harvesting of lung tissues on multiple days to determine viral load. For this reason, an animal model that allows live imaging of RSV in mice without the need to harvest lungs would allow following of individual animals at multiple time point following virus challenge to determine the efficacy of vaccines and therapeutics against RSV.

Methods: In this study, we developed a live imaging animal model using an RSV virus expressing firefly luciferase (FFL) to obtain real time information and follow virus dissemination from the nasal cavity to the lungs and increase in viral loads, after virus inoculation. This RSV whole body live imaging model is being used to evaluate vaccines and therapeutics. Mice were immunized with DS-Cav1 (kind gift from Peter Kwong, VRC, NIH), a pre-fusion F stabilized protein known to protect against RSV, or treated with PalivizuMab, the only licensed monoclonal antibody used to prevent severe RSV disease.

Results and Conclusion: Using live imaging, RSV-FFL (line 19F) was detected in the nasal cavities and lungs of mice. The luciferase signal was stronger in the lungs compared to the nose and peak titers were found on day 5 post-infection. The flux units measured in live imaging correlated with the lung viral load as measured by plaque assay.

To determine whether the live imaging model could be used to evaluate RSV vaccines, Balb/c mice were immunized with pre-fusion form of RSV-F (DS-Cav1) or mock vaccinated with PBS. Serum collected 10 days after the second immunization showed good neutralizing antibodies titers. Two weeks after vaccination, mice were infected with RSV-Line19F-FFL. DS-cav1 immunized mice had over 90% reduction in luciferase activity in the nose and lung cavity compared to the mock vaccinated mice.
To determine if this live imaging model can be used to evaluate RSV therapeutics, Palivizumab was administered intraperitoneally on day 2 post-RSV infection and mice were imaged daily. To compare luciferase activity to RSV viral load, lungs of mice were harvested on day 2 and 5 post-infection and homogenates were analyzed for plaque forming units and viral mRNA through plaque assay and qRT-PCR respectively. Palivizumab treated mice had over 40% reduction in luciferase activity in lungs and nasal cavity by day 5 post-infection.

We have developed an in vivo RSV imaging animal model that can reduce the number of mice used per experiment and provide real time information on the dissemination/replication of RSV in individual animals. Together with strong biostatistical tools this RSV live imaging animal model can be used for pre-clinical evaluation of novel RSV vaccine and therapeutics.

References:

Co-Delivery of Antigens Using a Novel Nanoparticle Pneumococcal Vaccine Induce Enhanced Immunogenicity in the Absence of Adjuvants

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Liquidia Technologies, Research Triangle Park, NC

Objective: Describe how PRINT® nanoparticle technology can be used to develop next generation conjugate Pneumococcal vaccines that allow for alternative carrier proteins, Pneumococcal specific, to be used in combination with protective pneumococcal polysaccharides to induce potent immune responses.

Background: PRINT® nanoparticle system is designed to imitate size and structural aspects of bacterial pathogens for the most efficient presentation and delivery of polysaccharide and protein antigens to elicit maximum immune responses. We have constructed defined PRINT® nanoparticle formulations of CRM197 and mutant pneumolysin protein (PLD) as carrier protein/immunogen with pneumococcal polysaccharides (PnPs) 1, 5, 14 using PRINT® nanoparticle system.

Methods: Preclinical immunization studies in BALB/c mice (n=6/group) were conducted to evaluate antibody (IgG) responses to the PRINT® vaccine candidates. Specifically, mice were vaccinated three times subcutaneously with various *PRINT formulations with defined compositions. Immunogenicity endpoints included antigen-specific (serotype/protein) IgG levels and opsonophagocytic killing assay calibrated against PCV13 responses.

Results and Conclusion: Nonadjuvated PRINT® particles elicited statistically robust anti-PnP1, 5, 14 antibody responses to both CRM197 and PLD carrier protein (≥ PCV13). PRINT® formulations show consistently strong correlations between serotype specific IgG titers and functional opsonophagocytic killing (OPK) responses. Depending on the formulation, strong anti-PLD immune responses were generated when compared to soluble PLD. Significantly, we have also demonstrated the ability of PLD not only to serve as an alternative carrier protein to CRM197 but also act as an effective immunogen in PRINT® formulations. Effective co-delivery of the polysaccharide and carrier protein together as components of PRINT® particles induces enhanced immunogenicity. Significantly, PLD as a carrier protein can also act as an effective immunogen when presented along with polysaccharides in PRINT® particles. PRINT® nanoparticle formulations hold potential for a low cost and simplified manufacturing path for multivalent particulated pneumococcal vaccines.

References:
SUBMITTED POSTER PRESENTATION ABSTRACTS
A Liposomal Formulation of NOD1 and NOD2 Agonists Reduces Lung Bacterial Burden in BCG-Primed CB6F1 Mice Challenged with Mycobacterium tuberculosis

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Objective: Explain the decrease in bacterial burden by a liposomal NOD agonist formulation is independent of an IFNg response.

Background: NOD receptors are a class of pattern recognition receptor (PRRs) that have been largely overshadowed by their toll like receptor (TLR) counterpart. NODs are unique in that they are not membrane bound receptors but exist in the cytosol where they can sense intracellular bacterial ligands. Additionally, when delivered with a lipophilic carrier, they have been shown to play a role in priming CD4+ T cells towards a Th1 profile lacking an IFNg response. Here we demonstrate that NOD agonists can be used to adjuvant immune responses and protect against an M. tuberculosis challenge.

Methods: CB6F1 mice were used in immunogenicity and aerosol challenge studies to evaluate a liposomal formulation of NOD agonists as an adjuvant to our current 5 antigen (Ag85B, ESAT6, Rv1733, Rv2626 and RpfD) recombinant protein (5Ag) vaccine. Adult female mice aged 10 weeks old were vaccinated with the 5Ag protein formulated with a NOD2 agonist (murabutide) and DDA or a combination of the NOD2 agonist, a NOD1 agonist (C12-iE-DAP) and DDA in the presence or absence of a BCG prime. Two additional groups of mice immunized with the 5Ag protein and a TLR3 agonist with or without a BCG prime were included as IFNg producing control groups. Immunogenicity in the absence of a BCG prime was evaluated by intracellular cytokine staining. Mice were challenged with 50-100 CFU of aerosolized M. tuberculosis Erdman strain. Spleens and lungs were used to determine viable bacterial load (CFU).

Results and Conclusion: Mice immunized with NOD agonists formulated in DDA elicited moderate TNF and IL2 responses while mice immunized with the TLR3 agonist elicited more robust Th1 cytokines including TNF, IL2 and IFNg. We observed a statistically significant reduction in lung CFU at 12 weeks post infection in mice primed with BCG and boosted with 5Ag, NOD1, NOD2, and DDA compared to BCG alone (one way ANOVA followed by Tukey’s post-test). There was no statistical difference in the bacterial burden of the TLR3 adjuvanted group and BCG alone. These data demonstrate that the combination of a BCG prime and boost with a liposomal formulation of 5Ag protein, C12-iE-DAP and murabutide lack the classical Th1 IFNg response while still reducing the bacterial burden compared to mice immunized with BCG alone.

References:

GPI-Anchored CCL28 as a Strong Mucosal Immunostimulator with Influenza VLPs

R. W. Compan, T. Mohan, B. Wang
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Objective: Explain how the membrane-anchored CCL28 containing HA VLPs provided systemic and mucosal protection in animals across distantly related subtypes.

Background: Influenza, with recurrent worldwide epidemics, presents a major health problem, affecting hundreds of millions of people with high morbidity and mortality. Because of the immunological regulations at the mucosa, protection provided at the pathogen’s entry site, higher levels of mucosal antibodies, cross-protection at mucosal surfaces, and promising results with different infectious diseases at mucosa, in both clinical and experimental settings, it would be advantageous to study the mucosal adjuvant with influenza antigens.
**Methods:** The GPI-CCL28 was engineered by fusing the coding sequences with the signal peptide from honeybee melittin to facilitate mCCL28 expression and the murine CD59 glycolipid-anchoring fragment to provide membrane anchoring. The M1, HA/M1, HA/M1/GPI-CCL28 VLPs were prepared by co-infecting sf9 insect cells with rBVs expressing M1, HA and GPI-CCL28 at optimum MOIs. Protein profiles of VLPs were analyzed by SDS-PAGE coupled with silver staining and western blot using antibodies against appropriate antigens. We also confirmed the quality and purity of VLP preparations by transmission electron microscopy (TEM). The surface expression and in-vitro chemotactic activity towards CCR3+/CCR10+cells of GPI-CCL28 were checked using flowcytometry. Mice were immunized intranasally with 0.5µg of CCL28 (membrane bound or soluble) and 1µg of HA antigens per animals. The IgG/IgA antibody responses were investigated in sera, and different mucosal secretions such as tracheal, lung, and intestinal washes. For cellular immune response, we analyzed CD4+IFN-γ+cells for proliferation and CD8+CD107a+cells for cytolytic activities using FACS at spleen, lung, mediastinal lymph nodes, and peyer’s patches. The Th1/Th2 cytokine and IgG/IgA secreting cells were estimated using ELISPOT while total cytokines’ concentration were checked by sandwich ELISA. Protective efficacy was determined by challenge studies with live A/Aichi/2/1968/H3N2 or A/Philippines/2/1982/H3N2 viruses.

**Results and Conclusion:** Interestingly, HA/M1/GPI-CCL28 VLPs showed in-vitro chemotactic activity for CD3+/CCR3+/CCR10+cells and CD19+/CCR3+/CCR10+cells. The end point titer for IgG antibodies in sera ranged between 51200-102400 which was significantly (p < 0.0001) higher (4-5 fold) than HA VLPs alone or when VLPs were mixed with sCCL28. The end point titer for IgA antibodies reached up to 12800 in tracheal, and intestinal washes, significantly (p < 0.005) higher (5-6 fold) than other formulations. We found IgG2a was higher than IgG1, indicating Th1 type of immune responses. The HAI titer was significantly (p < 0.001) higher (3-5 fold) in antibodies not only in sera, but also in tracheal and intestinal washes using the vaccine formulations containing HA/M1/GPI-CCL28 VLPs. Flow data showed that HA/M1/GPI-CCL28 VLPs induced cell proliferation, but did not encourage cytolitic activities. During cytokine estimations, a high IFN-γ and IL-2 with low IL-4 and TNF-α were observed in HA/M1/GPI-CCL28 VLPs. The challenge studies revealed 100% and 80% animal survival with no significant body weight loss, in the group of HA VLPs containing GPI-CCL28 with homologous and drifted viruses respectively. The GPI-CCL28-containing influenza VLPs act as strong immunostimulator at both systemic and mucosal sites when compared with influenza VLPs without CCL28, or influenza VLPs mixed with soluble CCL28 with the systemic and mucosal protection in animals across distantly related subtypes.

**References:**
pathway 1 and pathway 2, respectively. While peptide resistance maps to gp41 mutations, both pathways include non-overlapping sets of secondary mutations in gp120.

**Methods:** Here, we present our ongoing efforts to phenotypically characterize Envs from these two pathways. Using a lentiviral pseudovirus expression system, we have evaluated the infectivity, as well as sensitivity to nAbs, sCD4, and chemokine receptor inhibitors of Env proteins with defined N-peptide resistance mutations. Infectivity and sensitivity data were determined by single-round infectivity assays utilizing luciferase reporter gene expression in CD4+/CCR5+ target cells. Additional studies analyzing Envs from both pathways for neutralization against a panel of anti-Env nAbs, temperature sensitivity, stability, and Env incorporation have also been carried out or are ongoing.

**Results and Conclusion:** Our data confirm that these two resistance pathways are not equivalent. Neither pathway confers faster entry kinetics, with pathway 1 mutations in particular conferring significantly slower fusion kinetics than WT Env. Pathway 1 Envs appear to be more sensitive to sCD4 than WT and pathway 2 Envs. Pathway 1 Envs also have increased infectivity on low CD4 target cells. Together, these facts suggest that pathway 1 Envs have an increased capacity to utilize CD4 that has evolved with and may play a role in N-peptide resistance via this pathway.

**References:**


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**P4**

Design and Characterization of Bacterially Expressed Hemagglutinin Head Domain Immunogens
S. Swaroop, V. Mallajosyula, R. Varadarajan
Indian Institute of Science, Bangalore, India

**Objective:** Discuss the design of immunogens which can be bacterially expressed and are well folded and resistant to aggregation.

**Background:** Influenza infections result in 250,000 to 500,000 deaths annually. There is an urgent need to develop vaccines which elicit broadly neutralizing antibody (NAb) responses and can be manufactured rapidly. NAbs are generated against hemagglutinin (HA), the major surface glycoprotein of the influenza virus. NAbs against the exposed, immunodominant head domain of HA have higher potency, but lower breadth relative to those against the stem domain. In this study, we aim to rationally design HA head domain based subunit immunogens with mutations introduced to stabilize the fragment protein against aggregation.

**Methods:** We computationally delineated the interaction network in the HA head domain of H1N1 A/Puerto Rico/8/34 (PR/34) HA and used Rosetta Design to generate energy-minimized models to evaluate the designed mutations. Synthetic genes for the immunogens were cloned into the bacterial expression vector pET-15b. Solubility of the protein was assessed by SDS-PAGE. The folded nature of the protein was studied by circular dichroism (CD) and fluorescence spectroscopy. Binding of purified immunogens with HA head domain specific antibodies was probed by ELISA, surface plasmon resonance (SPR), and biolayer interferometry (BLI).

**Results and Conclusion:** We successfully engineered a head-domain fragment from influenza A H1N1 PR/34 that mimicked the native conformation. The rationally introduced mutations enhanced the solubility of the designed immunogen with respect to the wild-type fragment. Biophysical characterization indicated that the protein was stable and well-folded. The designed immunogen also exhibited an improved binding profile to the head-directed neutralizing antibodies WC00022 and WC00005 binding within the ‘Sa’ and ‘Sb’ antigenic sites of H1N1 PR/34 HA respectively, as opposed to the wild-type protein. The design principle was successfully extended to develop a head fragment immunogen from the pandemic H1N1 A/California/07/2009 (Ca/09). To conclude, A rationally
designed HA head domain based immunogen was generated which had improved solubility and antibody binding profile as compared to the wild-type fragment which lacks rational mutations.

References:

P5

Design and Stabilization of Stem Derived Immunogens from HA of Influenza A Viruses
T. Ahmad Najar, R. Varadarajan
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Objective: Discuss the recent developments in the field of subunit vaccine design against influenza viruses.

Background: Influenza virus, a human pathogen, is responsible for 250,000 to 500,000 deaths every year in addition to millions of hospitalizations world-wide. The virus evades the host immune response mainly by “antigenic drift” and occasionally by “antigenic shift” hence necessitating the need for annual reformulation of currently available vaccines. In addition, current vaccines such as live attenuated/inactivated vaccines are produced by laborious procedures of virus growth in embryonated chicken eggs hindering the rapid scale up during pandemic outbreaks. Hence a subunit vaccine providing heterosubtypic protection is highly desirable to combat the infection. In the recent past, several bnAbs have been isolated that target the conserved stem domain of HA thus making it an attractive target for universal vaccine candidate. However, the metastable conformation of this domain imposes challenges in designing a stable, independently folding HA stem immunogen.

Methods: To overcome the aforementioned challenges, a protein minimization approach was used to design headless stem immunogens, mimicking the epitopes of stem-directed bnAbs, capable of eliciting a broadly protective immune response. To further stabilize and increase the breadth of these stem-derived immunogens, a random mutagenesis library was constructed and displayed on the yeast cell surface to isolate mutants with improved stability and binding to bnAbs.

Results and Conclusion: In the present work, we have rationally designed stem-fragment immunogens from both group-1 and group-2 influenza viruses, which mimic the native-HA stem conformation and bind with high affinity to conformation specific bnAbs. These immunogens conferred robust subtype specific and modest heterosubtypic protection against lethal viral challenge in vivo. Biophysical and biochemical properties of one construct from group-1 viruses (H1HA6) was further improved by constructing a random mutagenesis library by error prone PCR using modified nucleotide analogues. The library was displayed on the yeast cell surface and after several rounds of sort and enrichment, one mutant clone (H1HA6P2) differing by two mutations from the wild-type protein was isolated. This mutant showed significant improvement in biophysical and biochemical properties as well as binding to bnAbs (CR6261, FI6v3, and F10) compared to the wild-type protein. The mutant protein (H1HA6P2) attained a neutral pH, native-like trimeric conformation in solution, is well folded and thermostable compared to the wild-type protein. Hence, it is a potential candidate for eliciting stem directed bnAbs.

References:
Mechanisms of Immunogenicity Provided by Eilat Virus-Based Vaccines

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Objective: Explain potential mechanisms of enhanced immunogenicity provided by the Eilat virus vaccine vector platform.

Background: Eilat virus (EILV) is an alphavirus isolated from a pool of mosquitoes collected in Israel. It replicates efficiently in insect cells but is unable to replicate in vertebrate cells. EILV is host-restricted in at least two points in its replication cycle: 1) attachment/entry, and 2) viral RNA replication. Our central hypothesis is that a chimeric alphavirus containing the non-structural protein genes of EILV and the structural protein genes of pathogenic alphaviruses, such as chikungunya (CHIKV) or Venezuelan equine encephalitis viruses (VEEV), will acquire the ability to attach and enter vertebrate cells via receptor-mediated endocytosis and deliver an RNA genome that is only capable of replication in insect cells, and provide for a safe and effective vaccine.

Methods: To test this hypothesis, we generated chimeric EILV/CHIKV and EILV/VEEV infectious cDNAs as well as various luciferase-based reporters using standard cloning techniques, and rescued the viruses in insect cells. We then performed cryo-electron microscopy (EM) of purified particles to assess structural characteristics, thin-section EM of EILV chimera-infected vertebrate cells to capture early entry events, luciferase-based reporter assays to evaluate genome delivery in vertebrate cells, and safety and immunogenicity studies in mice comparing EILV chimeras to formalin-inactivated and UV-inactivated preparations of vaccines.

Results and Conclusion: We found that EILV chimeras are structurally identical to their pathogenic counterparts, can enter vertebrate cells via clathrin-mediated endocytosis, deliver RNA, and provide superior immune responses to formalin-inactivated virus in mice while retaining a host-restricted replication phenotype in vivo. Finally, we performed an immunogenicity and efficacy study in non-human primates vaccinated with a single dose of EILV/CHIKV and demonstrated rapid seroconversion with high titer neutralizing antibody titers followed by complete protection against challenge with CHIKV.

Reference:

Probing the Humoral Immune Response against Respiratory Syncytial Virus to Guide Rational Vaccine Design

J. S. McLellan
Geisel School of Medicine at Dartmouth, Norwich, VT

Objective: Discuss how structure-based design has led to the development of promising RSV vaccine antigens and how characterization of the humoral response against RSV can lead to novel or improved vaccine candidates.

Background: Respiratory syncytial virus (RSV) causes acute lower respiratory tract infections that result in substantial morbidity and mortality in infants and the elderly. We believe that vaccine development can be guided by characterizing the spectrum of antibodies that each target population can elicit, and then designing vaccine antigens to preferentially induce the most protective antibodies. For RSV, it is generally agreed that an effective vaccine should elicit neutralizing antibodies against the viral fusion glycoprotein (RSV F). However, we are only just beginning to understand the breadth and properties of antibodies that the human immune system can generate against RSV F. Previously, we determined X-ray crystal structures of the prefusion (pre-F) and postfusion (post-F) conformations of RSV F, and using the structural information we engineered a soluble, prefusion-stabilized RSV F protein that elicited high neutralizing titers in mice and rhesus macaques, and provided proof-of-principle for structure-based vaccine design.

Methods: To inform the design of new or improved antigens, we have begun characterizing the antibody response to RSV F at a molecular level. Using pre-F and post-F to sort memory B cells from RSV-infected infants and adults, we have cloned and characterized hundreds of RSV F-specific antibodies representative of responses.
to natural infection. For each antibody, we have determined its neutralization potency and its binding affinity for pre-F and post-F.

**Results and Conclusion:** From these data, we have learned that infants can generate potent neutralizing antibodies, including some that lack somatic hypermutation. Competition mapping studies have identified several novel neutralizing antigenic sites in addition to the five known sites\(^4,5\) on RSV F that could serve as new targets for epitope-focused vaccine antigen design. The results from these studies are expected to guide the development of safe and effective RSV vaccines and create a platform of reagents and technologies to rapidly assess vaccine performance in future clinical trials.

**References:**

**Analytics for High Throughput (HT) Vaccine Antigen Characterization**

**P8**

**P. Ahl, J. Blue, H. Mach, S. McClure, C. Wang**  
Merck & Co., Inc.

**Objective:** Identify two novel analytical technologies suitable for HT Vaccine formulation development.

**Background:** Our goal is to improve the vaccine formulation development process by incorporating high throughput formulation development (HTFD) into the early vaccine development program. Vaccine HTFD will increase the ability to screen for stability dramatically more vaccine formulations (> 250 formulations) in much less time (< 1M) with significantly less antigen. HTFD alone cannot confirm the optimal vaccine drug product formulation for both efficacy and stability. However, by rapidly examining increased amounts of formulation conditions and excipients, HTFD should give a better understanding of the formulation input factors that impact vaccine drug product stability and identify a vaccine formulation design space that might result in optimal stability.

**Methods:** We have focused on two HT analytical technologies, differential scanning fluorimetry (DSF) and dynamic light scanning (DLS). These technologies are particularly well suited for quickly comparing the thermal stability of a large number of protein antigen formulations. DSF, with extrinsic fluorescence dyes such as Sypro Orange™ and Proteostat™, is an excellent method to establish the unfolding (Tm) and aggregation temperatures (Tagg) of protein antigens. Proteostat™ can even measure Tagg in the presence of formulation surfactants. The vaccine formulation composition can influence both Tm & Tagg. Formulations with high Tm & Tagg are typically the most thermally stable.

**Results and Conclusion:** Screening utilizing DSF pH and ionic strength screens were successfully completed in 96 well plates for three model antigens (AgA, AgC, and AgC). DLS temperature scans were used to directly measure the aggregation onset temperature of a model antigen with or without surfactants. DLS technology provided an excellent orthogonal HT stability assay to DSF measurements of antigen unfolding and aggregation. We have shown that these HT analytical technologies are well suited for vaccine formulation development.

**Reference:**
A Phase II Randomized Controlled Trial of an RSV F Nanoparticle Vaccine in Older Adults: Epidemiology and Efficacy

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Objective: Explain the epidemiology, immunogenicity, and efficacy results seen in the Phase II trial of a RSV F Nanoparticle Vaccine.

Background: Accelerated RSV vaccine development is underway to address the substantial unmet public health burden of RSV-associated hospitalizations and mortality among older adults in the US. In four phase I and II clinical trials in adults, the RSV F Vaccine was found to have an acceptable safety profile and to elicit robust anti-F IgG, Palivizumab-competing antibody (PCA), and microneutralization antibody responses.

Methods: The primary objectives of the randomized, observer-blinded, placebo-controlled, US-based Phase II trial were to: evaluate the safety and tolerability of RSV F Vaccine in adults ≥60 years of age, examine the amplitude and duration of anti-F IgG responses, and to describe the incidence of all symptomatic respiratory illness due to RSV among placebo recipients. The secondary and exploratory objectives were to evaluate the amplitude and duration of PCA and microneutralizing antibody responses, and to estimate the efficacy of the vaccine in the prevention of all symptomatic RSV respiratory illness in the older adult population respectively. Post-hoc analyses were conducted to estimate the efficacy of the vaccine in the prevention of more severe RSV associated lower respiratory tract disease (RSV-LRTD) as defined by: RT-PCR confirmed RSV infection and ≥3 signs/symptoms of lower respiratory tract disease. Active and passive RSV surveillance included weekly telephone outreach and symptom-triggered specimen collection and RT-PCR testing for RSV. Subjects were followed for 364 days for safety and serology was collected at seven time points.

Results and Conclusion: In the intention to treat (ITT) population, 798 subjects were randomized to receive the RSV F Vaccine and an equal number were randomized to receive placebo. The vaccine was well-tolerated with placebo and vaccine recipients reporting similar proportions of adverse events (AEs) and serious adverse events (SAEs). Durable 4.8 and 5.2 fold increases in anti-F IgG and PCA antibody titers, respectively, were observed beginning at 14 days in RSV F Vaccine but not placebo recipients. The incidence rate of any symptomatic RSV among placebo recipients was 4.9%. The efficacy of the RSV F Vaccine in the prevention of symptomatic RSV disease and more severe RSV-LRTD was 41% [95% CI: 2-64%] and 64% [95% CI: 1-87%], respectively. Protection appeared to persist throughout an approximate 6-month season of documented RSV transmission.

The trial confirmed previous estimates of the incidence rate of symptomatic RSV disease among community dwelling older adults and was the first ever demonstration of statistically-significant efficacy of an RSV vaccine in any population.

Reference:
**Objective:** Discuss the confirmation and extension of the immunogenicity and safety data that were the basis for accelerated approval of bivalent rLP2086 in the United States using data from two pivotal phase III studies of bivalent rLP2086 in adolescents and young adults.

**Background:** *Neisseria meningitidis* is a leading cause of bacterial meningitis and septicemia in infants, adolescents, and young adults. This significant public health concern is further highlighted by recent serogroup B (MnB) outbreaks on US college campuses. Bivalent rLP2086 (MenB-fHBP; Trumenba®) was approved in October 2014 by the US Food and Drug Administration to protect against MnB disease in individuals aged 10-25 years, offering the potential to extend prevention of IMD beyond that provided by quadrivalent ACWY conjugate vaccines. Bivalent rLP2086, which targets the conserved, surface-exposed virulence factor LP2086 (a factor H binding protein [fHBP]), is composed of two recombinant LP2086 antigens, one each from subfamily A (A05) and B (B01). ACIP recommends vaccination with one of the two MnB vaccines in at-risk persons aged ≥10 years. In June 2015, ACIP further recommended providers consider vaccinating adolescents/young adults aged 16-23 years because of the peak in meningococcal disease in this age group.

**Methods:** We present data from two pivotal phase III trials to confirm and extend the immunogenicity and safety data that were the basis for accelerated approval in the United States. In study B1971009, healthy subjects aged 10– < 19 years were randomized to receive one of three lots of bivalent rLP2086 at 0, 2, and 6 months or hepatitis A virus vaccine at 0 and 6 months and saline at 2 months. In study B1971016, healthy subjects aged 18– < 26 years were randomized to receive bivalent rLP2086 or saline at 0, 2, and 6 months. Immune responses were assessed by serum bactericidal assays using human complement (hSBAs) with four primary MnB test strains (MnB strain PMB80 [fHBP variant A22], PMB2001 [A56], PMB2948 [B24], and PMB2707 [B44]), each expressing fHBP variants heterologous to the vaccine antigens. Immunogenicity endpoints included the proportion of subjects achieving a ≥4-fold increase in hSBA titers from baseline for each test strain and hSBA titers greater than or equal to the lower limit of assay quantitation for PMB80 [A22], PMB2001 [A56], PMB2948 [B24], and PMB2707 [B44] combined (i.e., composite response) after three doses.

**Results and Conclusion:** 2,693 subjects received one of three lots of bivalent rLP2086 in study B1971009. For test strains PMB80 [A22], PMB2001 [A56], PMB2948 [B24], and PMB2707 [B44], 73.8%, 84.8%, 56.2%, and 55.9% of subjects, respectively, receiving lot one achieved a four-fold rise in hSBA titer after dose two; 54.1% achieved a composite response one month after dose two. Responses rose to 83.2%, 90.2%, 79.8%, and 85.9%, respectively, one month after dose three; 83.5% achieved a composite response one month after dose three. 2,471 subjects received bivalent rLP2086 in study B1971016. For test strains PMB80 [A22], PMB2001 [A56], PMB2948 [B24], and PMB2707 [B44], 66.9%, 85.9%, 67.9%, and 55.5% of subjects, respectively, receiving bivalent rLP2086 achieved a four-fold rise in hSBA titer after dose two; 64.5% achieved a composite response one month after dose three. These responses rose to 80.5%, 90.0%, 79.3%, and 79.6% of subjects, respectively, after dose three; 84.9% achieved a composite response one month after dose three. Few serious adverse events were reported. In both studies, local reactogenicity was mainly mild or moderate in severity and did not increase with subsequent dosing. Bivalent rLP2086 (MenB-fHBP; Trumenba®) elicits robust bactericidal response rates to all four heterologous test strains after three doses, reflective of broad coverage across diverse MnB disease strains. Safety and reactogenicity of bivalent rLP086 was consistent with prior reports; bivalent rLP2086 is safe and tolerable for use in adolescents and young adults aged 10–25 years.

**References:**

**Objective:** Describe the increased economic burden of pertussis experienced by patients with preexisting asthma or COPD and why groups with chronic respiratory conditions may especially benefit from targeted Tdap vaccination strategies.

**Background:** Recent surveillance indicates a resurgence of pertussis in the US. In 2012, over 48,000 pertussis cases were reported to the Centers for Disease Control and Prevention, more than any year since 1955, with over half of all cases occurring in people aged ≥11 years. Individuals with chronic respiratory conditions such as asthma have been shown to be at higher risk for infection, although the relationship between chronic respiratory diseases and the burden of pertussis remains uncharacterized. The present study examined the economic burden of pertussis among US adolescents and adults with asthma or chronic obstructive pulmonary disease (COPD) by comparing costs of diagnosed pertussis in patients with preexisting asthma or COPD to matched cohorts of patients without these conditions.

**Methods:** Retrospective analysis of administrative claims from the MarketScan Commercial Claims and Encounters and Medicare Supplemental (1/2006-6/2014) and Medicaid Multi-State (1/2007-12/2013) databases. These databases contain information on inpatient, outpatient, and pharmacy claims. All patients were required to have an International Classification of Diseases (ICD)-9-CM diagnosis of pertussis. The index date was defined as the initial pertussis diagnosis date minus 15 days to allow for inclusion of care related to the pertussis diagnosis work-up. Patients were also required to have ≥6 months of continuous enrollment before and after the index date and be aged ≥11 years. Preexisting asthma and COPD were identified based on ICD-9-CM diagnosis and prescriptions before the index date. Patients with preexisting asthma or COPD were matched 1:1 to patients without these conditions. All-cause and pertussis-related costs during the 3-month pre- and post-index periods were calculated; the differences from pre- to post-index date (“incremental” costs) were reported for cases and controls. The incremental difference was the difference in incremental costs between cases and controls. Multivariate regressions were used to estimate adjusted incremental costs.

**Results and Conclusion:** A total of 1,041 patients with asthma and 343 patients with COPD were matched to an equal number of controls without these conditions. The mean (standard deviation) age of the asthma and COPD cohorts was 32.1 (19.5) and 53.2 (18.4) years, with females comprising 63.6% and 63.0%, respectively. The highest proportion of pertussis diagnoses occurred in 2012. For patients with asthma, adjusted all-cause incremental costs increased by $2,189 in the 3 months post-index compared to $889 for controls (incremental difference=$1,301; p < 0.01); adjusted pertussis-related costs averaged $572 for cases versus $332 for controls (difference=$241; p < 0.01). Similarly, patients with COPD accrued $5,166 more in adjusted all-cause incremental costs in the 3 months post-index compared to $993 for controls (incremental difference=$4,173; p < 0.01); adjusted pertussis-related costs averaged $1,130 for cases versus $695 for controls (difference=$435; p < 0.01). This analysis found substantial increases in adjusted incremental costs (both overall and pertussis-related) during the 3 months post-pertussis for patients with either preexisting asthma or COPD compared to controls. These results highlight an increased economic burden of pertussis in people with asthma or COPD, who may benefit from tetanus-diphtheria-acellular pertussis (Tdap) vaccination.

**References:**


Objective: Discuss the different types of life-course health effects that childhood vaccination may induce during adulthood.

Background: Vaccination has been shown to confer health effects on conditions other than those directly attributable to vaccination, including reductions in all-cause child mortality. Humoral immunity induced by infectious disease vaccines has been associated with pro-inflammatory and regulatory T cell responses involved in chronic disease pathology, but whether these effects translate into the long-term development of non-communicable diseases during adulthood remains unclear. While certain vaccines can confer lifelong adaptive immunity, ascertaining life-course health effects can be methodologically challenging due to extended exposure-disease latency periods, combined with difficulties in retrospectively ascertaining childhood vaccination history and identifying functional correlates of vaccine immunity. To generate a disease profiling study of prolonged immunomodulation effects, we mapped phenotypic associations and conducted a biomarker expression analysis using nationwide life-course data from UK children. Our overall goal was to determine whether childhood exposure to common vaccines was associated with differences in health and disease during adulthood.

Methods: We analyzed longitudinal data from UK subjects enrolled in the National Child Development and British Cohort Studies. Participants were followed from birth up to 46 years. Vaccination status by 16 years of age was determined during childhood study interviews, based on parental recall and medical records. This included vaccination against diphtheria, measles, poliomyelitis, pertussis, rubella, smallpox, tetanus, and BCG. Primary health endpoints were presentation of chronic disease (ICD-10 coded); and biomarker levels for lipid, carbohydrate and atherosclerotic activity. We estimated associations between phenotypic disease and vaccine exposure using adjusted multivariate binary regression with robust variance, correcting for multiple testing using Greenland’s Semi-Bayes approach. We determined mean differences in biomarker levels using adjusted linear regression. In all models, we controlled bias due to assignment of vaccination under non-randomized conditions using inverse probability weighting by propensity score. Scores were constructed using generalized boosted models (a non-parametric machine-learning regression technique) incorporating standard vaccine uptake predictors as model factors.

Results and Conclusion: To characterize phenotypic signatures of immunomodulation, we calculated 394 risk estimates for 83 groups of chronic diseases (n=19,806 subjects). We found children were at lower risk of presenting chronic disease during adulthood if vaccinated against poliomyelitis [Adjusted Odds Ratio (aOR)=0.71, 95% Confidence Interval (CI)=0.68-0.75], diphtheria [aOR=0.72, 95%CI=0.68-0.76], and tetanus [aOR=0.75, 95%CI=0.69-0.81]. Types of chronic diseases protected by vaccination [p < 0.05] included: diabetes mellitus, musculoskeletal-connective tissue (inflammatory polyarthropathis; arthrosis; and, other soft-tissue disorders), and circulatory system diseases (ischemic heart disease; and arteries, arterioles, capillary disease). Results were validated using biochemical markers in a study sub-group (n=9,368). We found polio and diphtheria vaccination protective [p < 0.05] against dysregulated glucose metabolism (hypoglycaemia, diabetes, and glycaemic diabetes control). Biochemical differences [p < 0.05] linked to polio vaccination were closely aligned with lower risks of cardiovascular events (i.e., higher HDL levels and lower triglycerides, cholesterol, LDL, Tissue Plasminogen Activator, fibrinogen, C-reactive protein, and Von Willibrand factor). Our findings suggest shared mechanistic links between immunomodulation and metabolic syndrome, and potential roles for musculoskeletal-connective tissue system diseases. These findings may lead to a better understanding of underlying mechanisms of chronic disease development, helping to identify new avenues of use for childhood vaccination.

References:
Objectives: Describe the prevalence of high-risk HPV types specific to the 4vHPV and the 9vHPV vaccine among adult women in the United States. Quantify the impact of the 9vHPV vaccine on the prevalence of high-risk HPV types not covered with the 4vHPV vaccine among females. Specify variations in HPV types between females from different sociodemographic groups, and which groups will likely benefit most from the 9vHPV vaccine.

Background: The newly-approved 9-valent Human Papillomavirus (HPV) virus-like particle (9vHPV) vaccine will become the primary HPV vaccine administered in the US, as it can cover more HPV types. Estimating the prevalence of high-risk types specific to this vaccine among women is essential to understand reductions in HPV-related disease attributable to the 9vHPV vaccine in the future. Our purpose was to estimate the prevalence of high-risk HPV types specific to the quadrivalent (4vHPV) and 9vHPV vaccine using data from National Health and Nutrition Examination Survey (NHANES) 2009-2012.

Methods: This cross-sectional study included data from 3,474 women (20-59 years) with adequate vaginal samples from NHANES 2009-2012. We assessed prevalence of 14 types of high-risk HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) commonly detected by HPV DNA testing, 4vHPV high-risk types (HPV 16 and 18), and 5 additional 9vHPV specific high-risk types (HPV 31, 33, 45, 52, and 58), to examine the potential reduction in HPV prevalence when switching to the 9vHPV vaccine. We also examined the prevalence by age group.

Results and Conclusion: Prevalence of any high-risk type HPV was 21.3%, prevalence of 4vHPV high-risk types was 5.8%, prevalence of 9vHPV specific types was 7.3%, prevalence of non-4vHPV high-risk types was 18.4%, and prevalence of high-risk non-9vHPV types was 13.6%. Prevalence of 9vHPV specific types was 12.9% among young women (20-24 years), 13.4% in women 25-29 years, 6.8% in 30-39 years, 4.9% in 40-49 years, and 4.5% in 50-59 years, while prevalence of non-9vHPV high-risk types was 30.6%, 20.5%, 15.2%, 7.8%, and 6.5% in those age groups, respectively. High prevalence of 9vHPV specific types was observed in women 20-29 years, not currently married, non-Hispanic Blacks, current smokers, and women with ≥2 sex partners in the past year. Among women 20-24 years, 31.8% received at least one dose of HPV vaccine, and 18.1% completed the full 3-dose series. In Conclusion, the 4vHPV vaccine could reduce prevalence of high-risk types by 13.6% and the 9vHPV vaccine could reduce the prevalence by another 22.5%. Switching to the 9vHPV vaccine will greatly reduce the prevalence of high-risk types and related cancers. A quick and seamless introduction of the 9vHPV vaccine is needed, especially in high-prevalence groups, so that its benefit can be realized.

References:
Vaccinations against Smallpox and Tuberculosis Are Associated with Better Long-Term Survival: A Danish Observational Case-Cohort Study 1971-2010
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Objective: Explain the reason that vaccines with beneficial non-specific effects may reduce overall mortality even after the target diseases are eradicated.

Background: When vaccinations with vaccinia against smallpox and BCG against tuberculosis were phased out in some high-income countries around 1980, the impact on overall mortality was not examined. Recent studies from low-income countries have suggested that these vaccines are associated with significant mortality reductions, not explained by specific disease protection.¹-² Studies of non-specific effects of vaccines have primarily examined children, but studies in adults have also found that vaccinia and BCG were associated with lower mortality.³-⁴ We examined whether vaccinia and BCG administrated in childhood were associated with long-term mortality reductions in a high-income population.

Methods: In this case-cohort study, we followed 47,622 schoolchildren from Copenhagen, Denmark, born 1965 to 1976, from their first school health examination and to 2010. This cohort experienced the phase out of vaccinia and BCG vaccination programs.

Results and Conclusion: A sub-cohort of 5,316 individuals (699 excluded due to missing values) was followed for 164,450 person years (0.2% were lost to follow up), and 401 deaths due to natural causes (841 deaths in total) occurred in the full cohort. Compared with individuals who had not received vaccinia or BCG vaccination, those who had received both vaccinia and BCG had an adjusted hazard ratio (aHR) of 0.54 (95% confidence interval (CI): 0.36-0.81) for mortality due to natural causes of death; those who only received BCG had an aHR of 0.58 (95%CI: 0.39-0.85). Vaccinia and BCG were not associated with any protection against deaths by accidents, suicide or murder, the combined aHR being 0.94 (95%CI: 0.62-1.42). Vaccinia and BCG vaccinations were associated with better long-term survival, which was not explained by specific protection. Vaccines with beneficial non-specific effects may reduce overall mortality even after the target diseases are eradicated.

References:
Who Is the “Herd” in Herd Immunity?: How Herd Definition Affects Vaccination Coverage Rates and Herd Immunity Status

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Objective: Explain how variations in the definition of herds affect vaccine coverage calculations and the identification of communities at risk of vaccine-preventable disease outbreaks based on herd immunity status.

Background: Herd immunity occurs when a critical proportion of a population have immunity from an infectious disease, thereby protecting unvaccinated members of that population from disease transmission. The herd immunity threshold (HIT) is the minimum percentage of a population having immunity to prevent epidemics from occurring. Although the herd immunity concept is straightforward, evaluating a population’s herd immunity status is difficult in practice. Importantly, there is no generally accepted approach to define the herd or delineate a larger population into herds. We examine how variations in herd definition affect vaccine coverage calculations and the identification of at-risk communities based on herd immunity status.

Methods: Pertussis vaccination data from California schools were used to calculate coverage rates for kindergarteners in each US Census block (n=403,398). Multiple realizations of communities or “herds” were generated from these foundational data, ranging from small to large herds and including common community designations such as census tracts, counties, and school districts. Additional herd realizations were generated by grouping spatially contiguous regions with similar sociodemographic characteristics, including age distribution, race/ethnicity, and education. We calculated the pertussis vaccination coverage for each community and designated each as above or below the HIT, which falls between 91.7% and 94.4% for pertussis. We mapped and summarized the statewide proportion of kindergarteners in communities above and below the HIT and evaluated the sensitivity of individual communities to herd designation.

Results and Conclusion: The potentially at-risk population in California fluctuates substantially due to variation in herd definition. The percentage of kindergarteners residing in communities falling below the pertussis HIT ranged from 26-69% for the low HIT (91.7%) and from 72-89% for the high HIT (94.4%). Maps of California communities by HIT status exhibit considerable spatial variation across the different herd realizations. For many communities, HIT status is noticeably sensitive to which herd the community was assigned. Herd immunity status and the HIT are often used as benchmarks for childhood vaccine programs and public health interventions. This research indicates that the use of vaccination coverage rates and herd immunity status may not be a sufficient approach given the uncertainty in what constitutes a herd. Developing a more robust definition of the “herd” is crucial to identify at-risk communities and to implement more effective vaccine-related policies.

References:

Measles Immunity and Illness in Tianjin, China

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Objective: Describe the population characteristics of those individuals who are and those who are not susceptible to measles infection.

Background: Successful interruption of measles transmission requires high herd immunity of approximately 95%. Studies typically report vaccination coverage rather than population-level susceptibility when characterizing herd immunity although the latter is more informative in assessing control efforts. We examine multi-year incidence of measles and prevalence of measles antibodies in persons from Tianjin, China.

Methods: From 2011-15, we collected blood spots for measles testing from a population-based sample in Tianjin, China of 2,818 persons, including 1,200 aged 1-49 and 809 mother-infant pairs. We compare results from the measles serological testing to measles cases included in the disease surveillance system during that time.


Results and Conclusion: Overall, 72.7% of the sample tested positive for measles IgG antibodies. Most children 1-9 years (97.5%) tested IgG positive; the lowest levels of IgG positivity occurred in infants (37%) and individuals 30-39 years (81%). Vaccination-ineligible infants under age 8 months had 16.9% IgG positive and represented the age group with the greatest burden of disease (15.1% of cases). Testing results among the participants who were ≥9 months of age showed that seropositivity was comparable in males and females, and by rural, urban and, and suburban districts; by mother’s education level, and by participant education level for those > 18 years. In the multivariable logistic regression, age and vaccination status were significantly associated with measles IgG antibody status. The odds of positive IgG antibody status were 0.337 times as high for the unvaccinated compared to those vaccinated (95% CI: 0.217, 0.524). Children over age 1 year in Tianjin have a high level of herd immunity against measles. Infants and adults 30-39 years accounted for the majority of measles cases and have a level of herd immunity below the threshold required to interrupt measles transmission. Overall, the measles control program in Tianjin has been successful in reaching its target age group. China needs to increase measles herd immunity in adults while also preventing vaccine-ineligible infants from acquiring disease to realize national measles elimination goals.

Reference:

Developing Canadian Human Health Vaccine Priorities
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Objective: Explain the process undertaken in Canada to Identify priorities for human vaccines. Discuss Canada’s identified human health vaccine priorities.

Background: The Public Health Agency of Canada (PHAC) is mandated to protect the health of Canadians from infectious diseases. Immunization programs play an integral role in preventing infection, morbidity and mortality nationwide, and are a shared responsibility as Canada is a federated State. Canada is interested in targeting investments toward developing priority human health vaccines. In order to support priority vaccine development PHAC undertook a broad consultation with industry and public health professionals. We describe the consultation and results subsequently.

Methods: In 2012, a series of ten consultation workshops were initiated, with an aim to identify and prioritize vaccine-candidate pathogens against defined criteria, including: incidence; mortality; case fatality; communicability; treatability; clinical impact; public & political profile; ten-year projection of incidence; economic impact; and preventability. The results of these consultations were used as context for a structured survey distributed to the Canadian Council of Chief Medical Officers of Health (CCMOH), a federal, provincial, territorial expert body, in late 2014. Results were ranked and compared against the Global Vaccine Action Plan (GVAP).

Results and Conclusion: Through systematic consultations, we identified 16 candidate vaccines likely to emerge over the next six years, with six (38%) identified as having impacts on anti-microbial resistance (AMR). Nine candidate vaccines were identified as being medium term (7-12 years to production time), with three (33%) having AMR impacts. A final five candidate vaccines, including HIV, were identified as emerging over the longer-term (e.g., 13+ years), with all five having AMR impacts. These results informed a candidate-vaccine prioritization process, as was assessed by members of the CCMOH. The top five candidate vaccines from each category are presented. Short term: Influenza; RSV; Clostridium difficile; Streptococcus, Group A; Streptococcus pneumoniae. Medium term: Hepatitis C; Pertussis; Chlamydia trachomatis; S. aureus; Herpes simplex type 2. Long-term: HIV; universal influenza; Tuberculosis; Neisseria gonorrhoea; VRE. Nine (30%) of the candidate vaccines identified in this study are included in the GVAP, including seven (47%) from the five higher priority vaccines identified in each production timeline category. Conclusions With the development of vaccine priorities, the Federal Government is demonstrating leadership in promoting targeted vaccine development in the interests of Canadians. This data will support Canadian provinces, territories and industry alike in developing key vaccines for identified public health concerns.
Distinct Challenges in Cost-Effectiveness Analysis Modelling of HPV Vaccines in Low and Middle Income Countries: A Systematic Review

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Objectives: Learn that cost per vaccinated girl (CVG), vaccine coverage, and screening coverage are distinct parameters that could significantly affect cost-effectiveness analysis estimates of HPV vaccination in low and middle income countries. Understand that more precise parameters could be obtained by adapting cost analysis of HPV vaccine delivery conducted for other countries, observing the outcomes of cervical cancer screening programs in the same geographical region and by taking into account the country’s previous experience with other vaccination programs. Learn that incorporating herd immunity effect in cost-effectiveness analysis of HPV vaccine is essential in settings where high vaccine coverage is achievable, since it could significantly affect cost-effectiveness analysis estimates.

Background: Low and middle income countries (LMICs) face a number of challenges in implementing cervical cancer prevention programme that do not apply in high income countries. Therefore, if cost-effectiveness analyses (CEA) of HPV vaccination for LMICs are to make reliable CEA estimates and consequently appropriate policy advice, then they need to account for the distinct challenges that do not apply to high income countries. This review assessed distinct data and modeling challenges which face most of the LMICs and which could significantly alter model-based cost-effectiveness analysis estimates. The review specifically examines the following questions: (1) Does the existing HPV vaccination cost-effectiveness literature acknowledge the particular challenges of LMICs? (2) Is the uncertainty among the less readily available essential data/parameters regarding LMICs so large that the policy recommendations are affected? (3) How were the particular challenges accommodated in the models? (4) To what extent does vaccine coverage rate influence herd immunity effect and invariably policy recommendations?

Methods: The databases of MEDLINE, EMBASE, NHS Economic Evaluation Database, EconLit, Web of Science, and CEA Registry were searched for studies published since 2006. A descriptive, narrative, and interpretative synthesis of data was undertaken.

Results and Conclusion: Thirty three studies were included in the review. The majority of studies (n=26) acknowledged cost per vaccinated girl (CVG) and vaccine coverage rate as particular challenges for LMICs; while 10 studies identified screening coverage rate as a challenge. CVG, vaccine coverage and screening coverage were shown by some studies to significantly affect policy recommendations. While some studies addressed the considerable data uncertainties using sensitivity analyses, this resulted in ambiguous policy recommendations. Lastly, herd immunity effect was influential in high vaccine coverage scenarios. While many studies recognized aspects of the particular challenges of HPV vaccination in LMICs, greater efforts need to be made in adapting models to account for these challenges. Such include adapting cost analysis of HPV vaccine delivery conducted for other countries, observing the outcomes of cervical cancer screening programmes in the same geographical region and taking into account the country’s previous experience with other vaccination programmes. In settings where high vaccine coverage is achievable, it is essential to incorporate herd immunity effect.
An Opsonophagocytic Assay to Evaluate Immunogenicity of Non-Typhoidal *Salmonella* Vaccines

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**Objective:** Explain the new assays that measure functional activity of antibodies elicited by non-typhoidal Salmonella vaccines.

**Background:** Invasive non-typhoidal *Salmonella* (iNTS) infections comprise an important cause of morbidity and mortality in sub-Saharan Africa and several vaccines are in development to prevent these infections. Although different studies have evaluated anti-Salmonella serum bactericidal and opsonophagocytic antibody activity, assays that can routinely characterize functional antibody responses to Salmonella vaccines in a standardized manner have not been described.

**Methods:** We developed an NTS opsonophagocytic assay (OPA) based on the well-characterized pneumococcus OPA assay which measures killing of *S. Typhimurium* and *S. Enteritidis* using HL-60 phagocytic cells and baby rabbit complement. We compared OPA titers from mice immunized with live attenuated *S. Typhimurium* and *S. Enteritidis* vaccines with anti-LPS serum IgG titers using Spearman’s correlation co-efficient. We also examined seroconversion (greater than a four-fold rise compared to pre-immune serum) of OPA versus anti-LPS serum IgG titers.

**Results and Conclusion:** Using our optimized OPA assay, we observed significantly higher OPA titers of sera from mice immunized with live attenuated NTS vaccines compared to PBS. Additionally, we observed a significant correlation between OPA titer and anti-LPS serum IgG titer. All of the *S. Typhimurium*- and *S. Enteritidis*-vaccinated mice showed greater than a four-fold increase in OPA titers compared to pre-immune serum whereas only 20 of 21 *S. Typhimurium*-vaccinated mice and 19 of 20 *S. Enteritidis*-vaccinated mice seroconverted in terms of anti-LPS serum IgG titer. We developed a robust and reproducible assay to measure immune responses elicited by candidate NTS vaccines. Together with a complement-dependent serum bactericidal antibody (SBA) activity assay that we have previously described, the OPA assay described herein may be useful in determining NTS correlates of protection and could be used to guide vaccine development.

**References:**


Antigen Density Is a Critical Determinant of the Humoral Immune Response to Model Viral Antigens Displayed on a Nanoparticle Scaffold

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Objective: Explain how antigen density influences the magnitude of humoral immune responses to viral antigens displayed on the surface of synthetic nanoparticles.

Background: The development of effective vaccines for HIV-1 and pandemic influenza virus remains a major unmet human health need. We hypothesize that the display of the HIV-1 Envelope glycoprotein (Env) and the influenza hemagglutinin (HA) on the surface of a nanoparticle (NP) scaffold may contribute to this goal, since NP display has been shown to result in enhanced immune responses to several other viral antigens. We therefore designed a series of experiments to examine how the density of Env and HA display on a NP scaffold influences the magnitude and quality of the antigen-specific humoral immune response.

Methods: HIV-1 Env and Influenza A HA were displayed on the same NP scaffold at low, intermediate, and high density - corresponding to mean estimated antigen distances of 18, 13, and 10 nm on the NP surface. These distances were chosen to fall within the range of antigen distances encountered on the corresponding naturally occurring human viruses (mean antigen distance of 26 and 5 nm for influenza and HIV-1, respectively). The antigen-decorated NP were then evaluated for their ability to stimulate antigen specific B cell lines in vitro (as assessed by calcium flux). In addition, BALB/c mice were immunized with the antigen-decorated NP, and antigen-binding serum antibody titers were measured, along with the frequency of antigen-specific B cells.

Results and Conclusion: NP displaying a low density of Env or HA more efficiently stimulated antigen specific B cells in vitro, than did NP displaying a high antigen density. In addition, NP displaying Env or HA at low density also elicited higher titers of antigen-specific serum IgG in immunized mice, as well as an increased frequency of antigen-specific antibody secreting cells (ASC) in the spleen and bone marrow. Finally, low density display of HA also elicited higher serum titers of HA-inhibiting (HAI) antibodies in immunized mice. These studies show that the density of antigen on a NP scaffold is a critically important determinant of the magnitude and quality of the humoral immune response elicited, which is exemplified by an improved serological and cellular response to either HIV-1 Env or Influenza HA after vaccination of mice or treatment of antigen specific B cells with sparsely decorated NP compared to densely decorated NP. This study therefore suggests that high density display of antigen on a particulate scaffold may not always result in an optimal immune response.

References:
when the virus is highly pathogenic, this assay must be done under the appropriate level of containment; for select agents such as Ebola virus (EBOV), this is under Biological Safety Level 4 (BSL-4) conditions. Establishing neutralization assays for these viruses that can be done in BSL-2 laboratories will facilitate development of new vaccines.

Methods: Our approach uses a replication-competent hybrid virus whose genome carries the envelope gene from the pathogenic virus on the genetic backbone of a non-pathogenic virus. We use vesicular stomatitis virus (VSV), since VSV has the advantage that it can, once its own envelope gene is deleted, accommodate envelope genes from various viruses, express the heterologous envelope, and incorporate this envelope into the viral particle. The resulting chimeric virus uses the heterologous envelope for entry. We have constructed hybrid VSVs carrying the envelope genes for several species of EBOV. The readout for infectivity is by reverse transcriptase quantitative PCR, an approach we established for other viruses.\(^1\,2\) Importantly, the primers are directed against VSV rather than against the specific envelope gene.

Results and Conclusion: Infection kinetics of VSV.EBOV hybrid viruses at different input virus levels were determined on various cell lines, and the appropriate virus level was chosen to assess the neutralizing activity of various monoclonal and polyclonal antibodies with the hybrid viruses. We have shown that neutralization can be assessed within six hours after infection. The titer of neutralizing antibodies in our assay is being compared with the titer obtained in other assays. In conclusion, we have applied the VSV platform to quantify neutralizing antibodies to EBOV under BSL-2 conditions. However, because the readout for the assay is directed at the VSV genome, this platform should be directly applicable to any virus whose envelope is compatible with VSV biology. Having such a general platform should facilitate the introduction of neutralization assays for several viruses, which should accelerate the evaluation of vaccines against these agents.

References:

Highly Cross-Conserved Burkholderia T Cell Epitopes Generate Effector T Cell Responses in Vitro

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Objective: Illustrate how computational tools can be used to expedite the process of selecting T cell epitopes from whole genome databases and validating these epitopes in vitro using blood obtained from “naïve” human donors.

Background: Burkholderia pseudomallei and Burkholderia mallei cause glanders and melioidosis, respectively. Both are classified as Category B biothreat agents due to their high infectivity and potential use as a bioweapon. The related species Burkholderia cepaciae causes fatal ‘cepacia syndrome’ in cystic fibrosis patients, which is characterized by rapid deterioration, bacteremia, and necrotizing pneumonia. Clinical eradication of Burkholderia infection often fails due to antimicrobial resistance. Effective vaccination against Burkholderia infection is critically important to protect populations living in endemic areas worldwide and against bioterror threats. No vaccines or other prophylactics for these pathogens are available. Vaccines against Burkholderia should target cell-mediated immune response, which is believed to be essential to successfully clear Burkholderia infection. We hypothesize that a single vaccine comprising highly cross-conserved Burkholderia T cell epitopes might generate protective cell-mediated immune response against all the three species.

Methods: Immunoinformatics tools were used to identify immunogenic consensus sequences (ICS) that are enriched for promiscuous and highly conserved CD4+ T cell epitopes in all three Burkholderia species. The ICS peptides were validated in peripheral blood mononuclear cells (PBMCs) derived from healthy donors using
Wullner, et al. protocol with modification

**Results and Conclusion:** All of the peptides (100%) bound to at least two HLA alleles, 98% bound to at least three HLA alleles, 98% bound to at least four HLA alleles and 92% bound to all seven HLA alleles. The overall predictive accuracy was 81% (both positive and negative). Significant IFNγ response was induced by all peptides in at least one human donor as measured by IFNγ ELISpot assay. 86% of the peptide-specific IFNγ ELISpot responses were completely inhibited by antibody block of HLA-DR, indicating that these peptides are HLA-DR-restricted. Significant peptide-specific proliferation and Th1 cytokine production (IFNγ, TNFα and IL-2) in CD4+ T cells from healthy donors were observed in flow cytometry analysis. Immunoinformatics predictions, coupled with in vitro validation, can accelerate the selection of highly conserved T cell epitopes from genome sequence databases. The approach can be used for rapid selection of vaccine candidates for a wide array of emerging infectious diseases and biodefense targets.

**References:**

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**Identification of Pathogen Immunoevasion Triggers Using JanusMatrix: Implications for Vaccine Design**

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**Objective:** Illustrate how relationships with human sequences can impact the phenotype of T cell response to pathogen-derived T cell epitopes.

**Background:** Vaccines against many pathogens that cause chronic infection are unavailable, due largely to effective pathogen mechanisms for evading host immune responses. A novel escape mechanism observed in chronic viral infection is suppression of viral-specific effector CD4+ and CD8+ T cells through stimulation of regulatory T cells (Tregs). A significant T cell epitope property gaining wider attention is homology with host sequences. Viral epitopes with substantial homology to self may activate Tregs that suppress protective inflammatory responses and thereby enable viral persistence.

**Methods:** We designed an immunoinformatic algorithm, JanusMatrix, to identify such epitopes. For a pathogen-derived epitope, the algorithm searches the human genome for the same T cell receptor (TCR) face in 9mers that can bind human leukocyte antigens (HLA).¹

**Results and Conclusion:** Among published T cell epitopes in the IEDB, JanusMatrix successfully distinguishes IL-10 stimulating sequences (regulatory) from IL-4 stimulating sequences (effector). Additionally, we screened a wide range of human-host viruses for TCR-face similarity to self and discovered that chronic viruses generally appear more human-like than viruses that cause acute infection. We also discovered a promiscuous class II epitope located within non-structural hepatitis C virus (HCV) protein p7 cross-conserved with hundreds of human sequences. The epitope induces an increase in CD4+CD25+FoxP3+ Treg number and function in peripheral blood leukocyte cultures derived from an HLA-diverse cohort of HCV-infected patients, but not in cultures derived from patients who spontaneously cleared HCV or from non-infected individuals.² Similar patterns have been observed in HIV.³ Homology with the human genome represents a novel means by which viruses that seek to establish chronic infection escape human immunity and ensure their survival. Better classification of viral T cell epitopes as either effector or regulatory will improve the design of vaccines against chronic viruses to focus immune responses on protective mechanisms and avoid immunosuppression.
References:

Programming Anti-Tumor Immunity through Self-Assembly of Molecular Adjuvants
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Objective: Explain how programming anti-tumor immunity through self-assembly of molecular adjuvants is impacting cancer vaccine development.

Background: Cancer vaccines would benefit from programmable control over specific immune pathways – capabilities that could improve potency while also minimizing risks of current immunotherapies associated with autoimmune diseases. Traditional vaccines are often formulated with mixtures of adjuvants, antigens, and excipients which may each contribute to the type of immune response that arises. We hypothesize that self-assembly of electrostatic immune signals into immune polyelectrolyte multilayers (iPEMs) might provide a route for generation of simple, well-defined, and potent cancer vaccines with advantageous characteristics of tunable sizes, co-delivery, and maintaining functional immune signals.

Methods: iPEMs were assembled from PolyIC, a toll-like receptor (TLR) 3 agonist, and ether a model antigen (SIINFEKL) or a human melanoma antigen (hgp100), modified with cationic components to mediate iPEM assembly. Mice were immunized intra-dermally. SIINFEKL and hgp100-specific T cells were measured using MHC-I tetramer. For tumor studies, mice were challenged with B16-OVA or B16-F10. At terminal time points, T cell phenotypes were analyzed in LNs and tumors. Statistical analysis was carried out using one-way ANOVA test and survival analysis using Logrank test.

Results and Conclusion: iPEM capsule size was tunable and these materials offered programmable activation of antigen presentation and TLR signaling. Tumor challenge in mice with B16-OVA cells revealed a significant increase in median survival: 25, 16, and 13 days for mice immunized with polyIC/SIINFEKL iPEM capsules, soluble vaccine, and untreated mice (p < 0.001), respectively. iPEMs were next assembled from polyIC and a clinically relevant human melanoma antigen (hgp100). In a B16-F10 tumor model, mice immunized with polyIC/hgp100 iPEM capsules exhibited a significant increase in median survival with a value of 23.5 day, and 17.5 day and 16.5 days for admixed vaccines and untreated mice respectively (p < 0.05). These effects were mediated not only by expansion of antigen-specific CD8 T cells, but also through reduced regulatory T cells (Tregs) and CD8+ PD1+ T cells in draining LNs and tumors compared to untreated groups. iPEMs generate functional, tumor-specific T cell responses in mice and could serve as a simple, modular platform for studying and programming immunity without compromising the immune system. Future studies will focus on generating iPEMs with different TLRas allowing control of specific responses and investigation of the impact of T cell phenotype in LNs and tumors.

Reference:
**P25**

**Objective:** Describe the advantages of using RT-qPCR in high throughput assays to measure virus neutralization.

**Background:** Human cytomegalovirus (HCMV) is a leading cause of congenital infection that can result in serious disabilities in affected children. To facilitate HCMV vaccine development, a microscale neutralization assay based on reverse transcription quantitative PCR (RT-qPCR) was developed to quantify HCMV-neutralizing antibodies. Our approach relies on the generation of crude lysates from virus-infected cells that are amenable to direct analysis by RT-qPCR, thereby circumventing rate-limiting procedures associated with sample RNA extraction and purification.

**Methods:** By serial passaging of the laboratory HCMV strain AD169 in epithelial cells (ARPE-19), a revertant virus with restored epithelial cell tropism, designated AD169wt131, was obtained. AD169 and AD169wt131 were evaluated in both epithelial cells (ARPE-19) and fibroblasts (MRC-5) by one-step RT-qPCR targeting the immediate-early gene IE1 transcript of HCMV. Human serum samples (n=30) from healthy donors were tested for HCMV-specific IgG using a commercially available ELISA and for HCMV-neutralizing activity using our RT-qPCR-based neutralization assay.

**Results and Conclusion:** Expression kinetics indicated that RT-qPCR assessment could be conducted as early as 6 hours post-infection. In agreement with the ELISA results, higher neutralizing activity was observed in the HCMV IgG seropositive group when compared with the HCMV IgG seronegative group. In addition, HCMV IgG seropositive human sera exhibited higher neutralizing titers using epithelial cells compared with using fibroblasts (geometric mean titers of 344 and 8 in ARPE-19 cells and MRC-5 cells, respectively). Our assay was robust to variation in input virus dose. In addition, a simple lysis buffer containing a non-ionic detergent was successfully demonstrated to be a less costly alternative to commercial reagents for cell-lysate preparation. We have demonstrated the feasibility of using an endpoint assessment based on RT-qPCR performed on crude lysates from infected cells to measure neutralizing activity against HCMV in both epithelial cells and fibroblasts. Neutralization titers associated with HCMV IgG positive human sera were substantially higher when measured using epithelial cells compared with using fibroblasts, thus highlighting the need for an assay platform flexible enough to accommodate multiple cell types. Vaccine development may be facilitated by high throughput assays, such as our own, that are capable of measuring cell-type dependent HCMV-neutralizing activity while maintaining desirable features in terms of simplicity, rapidity, robustness, flexibility, and inter-laboratory transferability.

**References:**


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**P26**

**Objective:** Explain the importance of cell-mediated response in protection against S. aureus soft tissue and skin infection.
Background: *Staphylococcus aureus* is the leading cause of skin infection and certain invasive diseases. There is an urgent need to develop an effective vaccine to prevent *S. aureus* infections. However, recent failure in human vaccine trials, despite immunogenicity has indicated that an *S. aureus* vaccine has not yet been identified.

**Methods:** We tested a putative stress response protein, SACOL1789, as a vaccine candidate against *S. aureus* infection in the murine soft tissue and skin infection (SSTI) and bacteremia models. Seven weeks old BALB/c and B-cell deficient (BKO) BALB/c mice were immunized on d0 and d21. Blood serum was collected on d35 for ELISA analysis prior to infection.

**Results and Conclusion:** We found that immunization of SACOL1789 protects BALB/c mice with decreased lesion size and reduced bacterial load compared with controls. However, protection was not observed in the bacteremia model. We further evaluated whether protection in the SSTI model can be replicated in B cell deficient (BKO) BALB/c mice. Protection observed in BKO BALB/c mice indicated that B cells are not essential. We performed ELIspot on splenocytes extracted from immunized mice and detected increased levels of IL-4, but not IFN-g and IL-17A. This suggests that SACOL1789-driven protection is dependent on IL-4 production and possibly the IL-4 dependent Th2 cell-mediated pathway. It further suggests that immunogenicity alone will not identify candidate protective antigens and that antigens protective against SSTI may not be identical to those protecting against bacteremia.

**References:**


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**P27 Predicting Relatedness of PRRSv Strains Based on Whole Genome T Cell Epitope Content**

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**Objective:** Explain how to predict relatedness of PRRSv strains based on T cell epitope content to aid in vaccine selection.

**Background:** PRRSv (Porcine Reproductive and Respiratory virus) is an enormous economic burden to pork producers. Like many RNA viruses, PRRSv has considerable genetic and antigenic variability that has made the disease difficult to prevent with standard vaccines and an efficacious, broadly cross-protective formulation has yet to be developed.1 While methods for comparing existing vaccines to PRRSv strains have been informative, the ‘whole gene’ approach fails to estimate cross-reactivity because it does not consider the T cell epitopes that are presented to the immune system, and whether they are conserved between the vaccine and the challenge strain. For that reason, we developed an Epitope Content Comparison (EpiCC) tool to better define the degree of conservation between PRRSv vaccines and circulating strains. We propose to use this tool to identify the best vaccine to use for herd-specific PRRSv outbreaks.

**Methods:** Using the EpiCC tool, equipped with the PigMatrix2 algorithm for prediction of Swine Leukocyte Antigen (SLA)-restricted epitopes, we screened complete genomes from 19 PRRSv strains and three modified live virus (MLV) vaccines for predicted to bind to common class I and class II SLA alleles. Epitopes were compared and an epitope-based relatedness score (EpiCC score) was calculated. A distance EpiCC score matrix was constructed and used to build an ‘epi-phylogenetic tree’ that depicts the relatedness between strains based on epitope content.
Results and Conclusion: The higher the EpiCC score, the higher the T cell epitope content, the more related the epitopes of two strains are and more potential of cross-protection. Based on their epitope content, strains were grouped in three clusters. Ingelvac MLV clustered with six strains, while Ingelvac ATP and Fostera were part of the same cluster that included five more strains. The remaining five strains formed a different cluster unrelated to any of the vaccines. Vaccines might confer different degrees of cross-protection to strains in the same cluster. EpiCC scores could be potentially used to classify PRRSV strains based on their T cell epitope content. EpiCC provides an objective approach to aid pork producers in vaccine selection when a PRRSv strain is introduced into a herd, and to select viral epitopes for incorporation into a PRRSV vaccine.

References:

P28
Clinical Trial Regulatory Compliance Challenges in Research Naïve Locations
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Objective: Explain the preparation and set up in relation to regulatory compliance when clinical trials are initiated in research naïve locations.

Background: More and more clinical trials are being conducted in the research naïve locations as there is a higher concentration of eligible and willing subjects to participate in the clinical trials in these regions. This trend has resulted in quick set ups of clinical sites, pharmacies, laboratories, and data centers around the world in regions with poor facilities, infrastructure, and logistical support. This poster highlights some of the regulatory challenges that we have observed as we have audited the clinical trials with sites in the research naïve locations.

Methods: The conclusions have been drawn from the findings and recommendations issued after several vaccine clinical trial audits that TRI Inc. personnel have conducted in several international locations over the period of last five years.

Results and Conclusion: Facilities: 24 hour supply of electricity is not standard for most of these sites; buildings are not designed with fire safety, emergency evacuation, or handicap access in mind; fire and flood safety of the trial documentation is usually an afterthought; storage and transportation of study product, biological samples, and trial documentation is not ideal. Documentation and Personnel: Personnel with GCP-ICH training and experience is scarce and quick trainings are often not very effective; lack of good documentation practices; there is a high incidence of data discrepancies and the resolution time of these discrepancies is often longer than usual; Challenges with Independent Review Board approval documentation and reporting; there have been high incidences of Informed Consent Form/Process issues; completion of Regulatory Files and Trial Master Files is almost always a challenge and is pushed to end of the trial. In conclusion, there needs to be a higher emphasis on the preparation, set up and personnel training, and appropriate resourcing in relation to regulatory compliance when clinical trials are initiated in research naïve locations.

References:
Facilitators and Barriers of HPV Vaccination in a Sample of Urban Young Men Who Have Sex with Men

H. B. Fontenot
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Objective: Describe YMSM’s thoughts and beliefs related to HPV vaccination as well as understand factors that may facilitate HPV vaccination among the YMSM community.

Background: Overall prevalence of HPV for men is roughly 40 to 50%. Rates of infection for men who have sex with men (MSM) are greater at 64% and above 90% for MSM who also are infected with HIV. HPV is associated with anal, penile and oropharyngeal cancers in men. To date, the majority of research has focused on female HPV vaccination; however it is predicted that by 2020 rates of certain HPV cancers primarily affecting men may exceed the national annual rates of cervical cancers. There is a dearth of studies examining factors related to HPV vaccination for men and in particular young MSM (YMSM). Therefore, the purpose of this study was to elicit YMSM’s beliefs about HPV and HPV vaccine as well as describe YMSM’s perceived barriers and facilitators of HPV vaccination initiation and completion.

Methods: A qualitative study with a focus group design was conducted from May 2014 to May 2015. One hour in-person focus groups were conducted in the Boston area with YMSM ages 18 to 23 years who were able to read and understand English. Participants were recruited primarily from an urban LGBTQ drop-in center, but also from an urban LGBTQ focused adolescent community health center, and by geo-location targeted advertisements on a mobile social networking app for MSM. The men completed a written questionnaire that gathered demographic information, general health patterns, and sexual health information. The focus groups utilized a semi-structured script that was designed to elicit participant knowledge, beliefs and perceptions about HPV and HPV vaccines with a focus on perceived facilitators and barriers to vaccination. The quantitative questionnaire data was analyzed using descriptive statistics, including the mean and standard deviations for continuous variables, and percentages for nominal data. The qualitative focus group data was analyzed using content analysis.

Results and Conclusion: The sample consisted of 34 YMSM with a mean age of 20.8 years. They identified their race/ethnicity as 23.5% White, 35.3% Black, 8.8% Asian, 2.9% American Indian, 23.5% more than one race, 6% other and 32.4% Hispanic Black/African-American. Four themes emerged from the data: general HPV knowledge, beliefs regarding vaccines and the HPV vaccine, stigma, and facilitators and barriers to HPV vaccination and completion. The participants were aware that the vaccine was available for men, but they demonstrated low levels of knowledge about male associated HPV diseases. They overwhelmingly viewed vaccines, in general, positively and after learning more about HPV the participants voiced support for the HPV vaccine for YMSM. The major concerns related to HPV vaccination were pain/ fear of injection and side effects. Participants described stigmas related to their sexual orientation, STD testing, and discussing health needs related to gay men. Finally, the participants believed the use of technology (mobile apps), combining HPV vaccination with other types of health visits, and increasing awareness would facilitate HPV vaccination among YMSMs. They also believed reminder systems and flexibility in dose scheduling would facilitate three-dose vaccine completion. The findings from this study help health providers understand YMSM’s perspectives on HPV vaccination, provide foundational knowledge towards building a patient-centered, culturally relevant vaccine interventions, and point to the importance of interventions that focus on the use of technology, bundling of HPV vaccination services with other types of health visits, and increasing HPV and HPV vaccine awareness among males and YMSM.

References:
Joint Frailty Mixed Models: Accounting for Heterogeneity in Sieve Analysis of Vaccine Efficacy
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Objectives: Articulate the “leaky vaccine” assumptions that hold when using current methods to answer questions of differential vaccine efficacy. Demonstrate the importance of using alternate models when the assumptions cannot be reasonably expected to hold.

Background: In randomized trials of preventative vaccines, we are often interested in whether efficacy differs based on some characteristic of the disease endpoint, such as the serotype of an infecting pathogen. It has been shown that evaluation of vaccine efficacy is sensitive to assumptions about the protective mechanism of the vaccine. Currently, statistical methods designed to test for differential efficacy across disease types (“sieve analysis”), assume that the effect of the vaccine is to reduce the risk of each disease type by the same factor for all treated participants (a homogeneous “leaky vaccine” model). Significant biases can occur in estimation and testing of vaccine efficacies when this assumption does not hold.

Methods: We propose a class of mixed models, incorporating subject-level random effects (“frailties”) to account for unobserved heterogeneity in participant response to vaccination. We make the simplifying assumption that, for each disease type, the vaccine provides complete immunity for some proportion of subjects, and partial protection to the rest. This model encompasses the leaky vaccine model, while also allowing for a wider variety of protective mechanisms. Estimating parameter values and testing for a sieve effect are straightforward procedures using readily available numeric optimization methods. We evaluate the reliability of our approach using simulation studies, and demonstrate its applicability in the context of dengue vaccine efficacy studies.

Results and Conclusion: Simulation results suggest that all parameters from the proposed model can be reliably estimated. Our approach performs comparably to existing methods in cases where the leaky vaccine assumption is appropriate, and favorably when the assumptions do not hold. In some cases, however, very large sample sizes are needed in order to distinguish between different plausible sets of parameters in the joint frailty model. We discuss the implications of such for the design and interpretation of efficacy studies. Despite some of the limitations and assumptions of frailty mixed models, we have demonstrated an approach to sieve analysis that improves upon current methodology by accounting for unobserved subject heterogeneity.

References:
Background: The use of neuraminidase-inhibiting anti-viral medication to treat influenza is relatively infrequent.\(^1\) Rapid, cost-effective methods for diagnosing influenza are needed. Multi-viral respiratory panels using reverse transcription polymerase chain reaction (PCR) assays to diagnose influenza are accurate but expensive and more time-consuming than low sensitivity rapid flu tests. Influenza clinical decision algorithms are both rapid and inexpensive, but most are based on regression analyses that do not account for higher order interactions. This study used classification and regression trees (CART) modeling to estimate probabilities of influenza.\(^2\)

Methods: Eligible enrollees ≥ 5 years old (n=4,173) who presented at ambulatory centers for treatment of acute respiratory illness (≤ 7 days) with cough or fever in 2011-12, provided nasal and pharyngeal swabs for PCR testing for influenza, information on demographics, symptoms, personal characteristics and self-reported influenza vaccination status.

Results and Conclusion: Antiviral medication was prescribed for just 15% of those with PCR-confirmed influenza. An algorithm that included fever, cough, fatigue, and either no household smoke or household smoke with no shortness of breath had a sensitivity of 81% and a specificity of 52% for the development sample. PPV was 24% and NPV was 94%. The algorithm based on CART recursive partitioning, can be used to estimate probability of influenza with good sensitivity and high NPV, but low PPV among outpatients ≥ 5 years. Further testing during additional influenza seasons may help to determine how this algorithm could be used in decision making for laboratory testing and antiviral use in patients with acute respiratory illness.

References:
develop effective HPV immunization programs and policies. The results will assist in eliminating barriers to the HPV vaccine among this high-risk group by increasing awareness of HPV and the HPV vaccine.

References:

P33 The Association of Health Seeking Behaviors with HPV Vaccination Status among High-Risk Urban Youth
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Objective: Describe disparities related to HPV vaccination as well as health-related behaviors that are positively associated with HPV vaccination among a diverse sample of at-risk urban youth.

Background: Vaccination is the primary preventative strategy to reduce the burden of human papillomavirus (HPV) related diseases in the United States (US). Recommendations for the HPV vaccine set by the Centers for Disease Control and Prevention are: routine HPV vaccination for all males and females ages 11-12 years with routine recommended ‘catch up’ vaccination for females through age 26 years and males through age 21 years (males may also obtain vaccination through age 26 years). In the US the HPV vaccination rates persist far below the national goal of 80% for males and females. Current research continues to monitor vaccination initiation and completion rates as well as uncover facilitators and barriers of vaccination. However, limited research has explored factors associated with HPV vaccination among the ‘catch up’ population including disadvantaged and high-risk males and females, as well as lesbian, gay, bisexual, transgender and queer (LGBTQ) youth. Therefore, this study was designed to assess HPV vaccination rates among a diverse sample of urban high-risk youth, and to assess the relationships between vaccination status and patient/health-related characteristics.

Methods: A retrospective electronic medical record review was conducted at an urban, homeless, and LGBTQ focused adolescent health center in northeastern United States. This study was guided by the Ecological Model which informed development of the data abstraction instrument. Data abstracted by investigators included: demographic/social characteristics, sexual/reproductive and general health behaviors, and HPV vaccine status. Logistic regression models examined the associations between vaccination and 1) demographic/social characteristics and 2) health behaviors.

Results and Conclusion: A total of 1,211 male and 1326 female medical records were reviewed from patients who presented for care between January 2010 and June 2013. Approximately 46% were Caucasian, their mean age was 21-22 years. About half of the sample (45% of males and 58% of females) identified as heterosexual and reported stable/secure housing (45% of males and 51% of females). Nine percent of males and 30% of females had obtained ≥ 1 HPV vaccine dose. In the regression models, age (p< .001) and education (p≤.05) were significantly associated with HPV vaccination. The strongest predictors of HPV vaccination were health-related behaviors: having an annual exam (Male p < .001, OR= 2.9; Female p < .001, OR= 2.6), or obtaining a non-HPV vaccine (Male p = .001, OR= 2.5; Female p = .001, OR= 1.9). For females, having had a pap test (p< .001, OR= 3.8) or a STI focus visit (p< .001, OR= 1.8) were also associated with an increase in odds of HPV vaccination. Among a high-risk adolescent sample, several health seeking behaviors increased the odds of HPV vaccination, reinforcing the importance of providers’ using annual or other routine exams, visits involving administration of other vaccines or STI screening as cues for HPV vaccination.
Gender and Ethnicity Are Important Characteristics for Inclusion and Analysis in Clinical Trials: An Annotated Bibliography

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Objective: Explain the challenges, barriers, and opportunities associated with achieving adequate representation by gender, race, and ethnicity in clinical trials including vaccine trials.

Background: Gender and ethnic disparities in clinical research and trials of new therapies remain a major challenge for biomedical research in the United States and other countries. We performed a systematic review of the literature to create an annotated bibliography to identify methods for future research that improve demographic representation in clinical trials including phase I, II, and III vaccine trials.

Methods: We identified peer-reviewed publications listed in PubMed and Google Scholar during the years 2000-15 using standardized search terms (e.g., clinical trial, gender, ethnic, representation, underrepresentation, and analysis). Studies were included in this review if they were published in English-language peer-reviewed publications. Studies were excluded if full-text was not available or if the publication date was before 2000. Studies were grouped into methodologic topic areas for comparison. Publications were reviewed and information abstracted for analysis with other publications obtained in this review.

Results and Conclusion: Following exclusion of studies, a total of 85 publications was identified that addressed topics in a) gender and ethnic representation disparities among enrolled study subjects, b) study recruitment strategies and c) journal publication of results by gender and racial/ethnic subgroups, d)___________. Our annotated review has several key findings: 1), participation rate among female and minority adults continues to be inadequately low, 2) analysis and report of safety, efficacy and effectiveness based on gender and ethnicity in clinical trial and other studies remains low, 3) pregnant women are routinely excluded from the vast majority of clinical trials. 4) differential mortality among males and females needs to be considered in the design and recruitment strategies for clinical trials. Despite suggestions from some authors that gender-based representation in trials has now achieve balance, there are persistent indications for the need to improve gender equity among study participants. Similarly, our review underscores the need to improve racial/ethnic minority representation in trials. Such efforts will require active programs that address key barriers including limited education, lack of health insurance, fear of harm and language difficulties.

References:
**Objective:** Determine if the metabolically attenuated *Shigella flexneri* vaccine candidates CVD 1213 and CVD 1215 induce correlates of protection in model systems.

**Background:** *Shigella flexneri*, a Gram-negative enteroinvasive bacterium, is a leading cause of diarrheal disease in children under the age of five in developing countries. The development of an efficacious vaccine has been elusive, in part due to the lack of in vitro correlates of protection and the requirement for serotype specific protection. The two new vaccine strains, CVD 1213 and CVD 1215 (derived from *S. flexneri* 3a and *S. flexneri* 6), represent two prominent *S. flexneri* serotypes. Combined with CVD 1208S, they could provide broad spectrum immunity against shigellosis. We have performed a series of in vitro and in vivo experiments to assess the ability of the new vaccine candidates to induce immune-associated responses utilizing the well-studied live, attenuated *Shigella flexneri* 2a vaccine CVD 1208S as a standard. A multi-valent vaccine may be necessary for broad-spectrum immunity; therefore the use of the new candidates in a mixed vaccine was also assessed.

**Methods:** Like CVD 1208S, each vaccine strain is attenuated with a deletion in the guaBA operon encoding critical enzymes of the de novo guanine biosynthesis pathway; confirmation of auxotrophy was performed using minimal media broth cultures with and without guanine. Host responses to Shigella vaccines were measured using in vitro methods that include: (1) macrophage cytotoxicity assays using differentiated THP-1 human macrophages, (2) gentamicin protection assays in human epithelial HT29 cells to assess invasion and replication rates, and (3) enzyme-linked immunosorbent assays (ELISA) to quantify cytokine secretion (specifically IL-8, CXCL-1, TNF-α, and IL-1β) from infected macrophages and epithelial cells. Additionally, in vivo studies in guinea pigs were performed to assess Shigella LPS-specific antibody response and protection against wild type challenge following immunization with each vaccine individually and as a tri-valent mixed vaccine.

**Results and Conclusion:** Genetic deletions were confirmed with PCR. Growth curves demonstrated that the vaccine candidates were guanine auxotrophs; without the presence of supplemental guanine, the vaccine strains were unable to grow. Wild-type growth was unaffected by the presence or absence of guanine in the media. Using the human HT-29 intestinal cell line, invasion by the vaccines was not significantly decreased compared to wild type; however, the attenuated vaccines were unable to replicate intracellularly. Limited concentrations of guanine in host cells results in attenuation of vaccine strain grown intracellularly. Interaction with a second important cell type, macrophages, was also assessed. Vaccine candidates demonstrated varied cytotoxic effects in human macrophages but remained comparable to their parental wild type strains. Cytokine secretion from macrophages and epithelial cells infected with the vaccines was consistent with secretion from wild type infected cells and significantly higher than uninfected cells. Guinea pig immunization studies revealed a robust induction of Shigella serotype specific LPS- specific IgA and IgG antibodies (100% seroconversion) following immunization with each individual vaccine strain and a mixture of all three. The guinea pig Sereny demonstrated protection against wild type *Shigella flexneri* serotypes 2a, 3a and 6 challenge with a mixed immunization including 1208S, 1213 and 1215. The in vitro host responses to the two new vaccine candidates are consistent with responses to the well-established CVD 1208S vaccine. Animal data demonstrates the vaccines’ protective capacity and immunogenicity singly and as a mixed vaccine. This indicates that CVD 1213 and CVD 1215 are viable candidates for the creation of a multivalent vaccine that could confer broad spectrum protection against *Shigella flexneri* infections.

**References:**
Characterization of the Highly Protective Live Attenuated Tularemia Vaccine Candidate, Schu S4ΔaroD

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Objectives: Define the need for a vaccine against Francisella tularensis. Explain why Schu S4ΔaroD is a suitable candidate for a live attenuated vaccine against this pathogen.

Background: Francisella tularensis subsp. tularensis (type A) (Ft) is a Tier One Select Agent and potential bioterrorism agent due to its low infectious dose (less than 10 CFU inhaled will cause pulmonary disease), high mortality rate (30-60% if untreated), ability to be spread via the aerosol route, and history of past weaponization. Vaccine development against this pathogen is a priority. The Live Vaccine Strain (LVS), derived from a type B (subsp. holarctica) strain, underwent extensive clinical trials in the 1960s where it was shown to confer only partial protection against virulent type A Ft challenge. Despite its suboptimal efficacy, LVS provides proof of principle that a live attenuated strain can generate protection against the highly human virulent subsp. tularensis. We developed a series of defined, live attenuated vaccines against Ft generated in the subsp. tularensis background strain Schu S4. One candidate, Schu S4ΔaroD, was highly protective against wild-type challenge.

Methods: An allelic exchange system was used to engineer an unmarked deletion in the aroD gene encoding 3-dehydroquinate, the third enzyme in the shikimate pathway for aromatic amino acid synthesis. This strain was tested for attenuation of virulence in vitro in macrophage replication assays and in vivo in the C57BL/6 mouse model. Its protective capacity was assessed against increasing intranasal (IN) doses of WT Schu S4 in mice using prime and prime-boost IN vaccination strategies. Organ bacterial burden and histopathology were assessed post-vaccination at defined time points in groups of mice receiving escalating doses of IN Schu S4ΔaroD. Additionally, cytokine gene transcription was measured in organs of these mice using qRT-PCR, and systemic humoral responses were determined by ELISA of serum from mice. We also assessed functional capacity of immune sera, using opsonophagocytosis assays. Immune cell infiltration was analyzed at defined time points post-vaccination using multi-color flow cytometry. We have begun to compare our protective vaccine candidate Schu S4ΔaroD to an attenuated, non-protective strain Schu S4ΔguaBA in these assays, which will help us to determine correlates of protection against Ft.

Results and Conclusion: Schu S4ΔaroD was attenuated for growth in vitro, both in broth and in murine macrophages (J774.A1 and primary peritoneal). It was also attenuated in vivo in mice (IN LD50 ~5x10⁵ CFU vs WT LD50 ~< 10 CFU). A single low-dose (50 CFU) intranasal (IN) Schu S4ΔaroD immunization was 80% protective against 100 CFU IN wild-type Schu S4 challenge, and when administered in a prime-boost regimen, Schu S4ΔaroD fully protected mice from high-dose (1000 CFU) Schu S4 IN challenge. Following IN vaccination in mice, peak organ cytokine induction, organ bacterial burden, and histopathology correlated in a dose-dependent manner based on initial inoculum. Mice produced a Th1-driven, IgG2c antibody response post-vaccination; this antibody controlled WT Schu S4 replication in classically activated (IFN-γ treated) J774 macrophages, but not untreated or alternatively activated (IL-4 treated) macrophages. Furthermore, IN vaccination with Schu S4ΔaroD induced differential cellular influx, notably, a significant increase in the amount of activated antigen presenting cells (dendritic cells and macrophages), within the lungs when compared to WT challenge or IN vaccination with the non-protective, live attenuated mutant Schu S4 ΔguaBA. In summary, Schu S4ΔaroD is a live attenuated Ft vaccine candidate that conferred protection against the highest challenge dose of virulent Ft Schu S4 that has been reported. We have also demonstrated this vaccine to be protective in our secondary animal model for tularemia, the New Zealand white rabbit. Differential immune responses following immunization with Schu S4ΔaroD compared to immune responses following IN administration of non-protective, attenuated strains like Schu S4ΔguaBA will allow identification of correlates of protection against Ft. Further pre-clinical assessment of Schu S4ΔaroD is ongoing in our laboratory.

References:
Cutaneous Deficiency of Filaggrin and STAT3 Exacerbates Vaccinia Disease in Vivo: Role of TGFbR Signaling

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Objectives: Describe the new model of eczema vaccinatum. Discuss the complexities of the cutaneous immune system in normal and abnormal states. Restate the potential for pharmacologic interventions in treating patients with these disorders.

Background: Concern that variola virus, the causative agent of smallpox, might be used as a biological weapon has prompted US stockpiling of live vaccinia virus vaccine. Vaccinated first responders, military personnel, and their close contacts can develop eczema vaccinatum (EV), a severe disseminated infection that occurs in some persons with atopic dermatitis (AD) or other skin disorders. AD is a chronic condition affecting approximately 10% of the US population, with prevalence reported at up to 20% in infants and young children. Should the US return to universal vaccination, thousands of EV cases are anticipated, which if untreated result in prolonged hospitalization, and a fatality rate of up to 40%. The only licensed treatment for EV is vaccinia immune globulin (VIG). Optimized dosing of VIG and identification of potential co-treatments are hampered by the lack of relevant, accessible animal models.

Methods: The overall goal of our studies is to develop an accessible animal model that captures the essential features of severe EV, which include prolonged, elevated vaccinia burden in the skin. This model could be used to increase understanding of cutaneous infection susceptibility in general, and to find alternative, dose-sparing strategies utilizing VIG, with or without adjuvant therapies. Toward this end, we performed vaccinia challenge studies using ACAM2000 as previously described, using mice with combined cutaneous deficiencies of filaggrin and STAT3, two genes associated with atopic dermatitis and susceptibility to severe skin infections. In this model, immunosuppressed, filaggrin-deficient mice received topical STAT3 inhibitor prior to scarification. We also infected cultured human keratinocytes with ACAM2000 and analyzed innate immune responses such as rapid programmed cell death and inflammatory cytokine release. The contributions of filaggrin, STAT3, and innate signaling molecules including RIP1, RIP3, MLKL, caspase-1, and DAI were evaluated using a combination of small molecule inhibitors and siRNA.

Results and Conclusion: Immunosuppressed, filaggrin-deficient mice that received topical STAT3 inhibitor prior to scarification with ACAM2000 demonstrated rapid weight loss, prolonged vaccinia burden in the skin, and extensive dermatitis, with accumulation of chymase-expressing mast cells (i.e., mucosal phenotype) and expansion of Sca-1+ semi-differentiated cells in the vaccinia lesion. The TGFb family ligand activin A was upregulated ten-fold in infected skin. Post-exposure, topical inhibition of activin receptor-like kinase 5 (ALK5; TGFbR1) signaling synergized with vaccinia immune globulin (VIG) to promote vaccinia clearance from the skin. The post-exposure co-treatment also limited weight loss, and accelerated wound resolution. In vitro studies confirmed that ACAM2000 infection triggered rapid programmed cell death (necroptosis), inflammatory cytokine release, and activin A secretion in cultured human keratinocytes. Rapid cell death and inflammatory cytokine release were dependent on RIP1, RIP3, MLKL, and the cytosolic viral DNA sensor DAI. Cultured keratinocytes treated with STAT3- or filaggrin-directed siRNA prior to infection demonstrated reduced cell death, reduced inflammatory cytokine release, and increased virus replication. Together these data point to novel roles of filaggrin and STAT3 in immediate antiviral responses in vaccinia-infected skin. Excessive signaling of activin A and/or other TGFb family ligands in skin may contribute to rapid cutaneous spread of vaccinia. Future studies will evaluate synergy of small-molecule antiviral therapies with VIG in this model, as well as potential VIG cotherapies to modulate wound healing responses in the skin. Future studies using this model may inform VIG dosing decisions, and should help to identify promising candidate molecules for EV treatment.

References:

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Objective: Evaluate the advantage of bioimaging over traditional methods for assessment of viral loads for testing of antiviral therapies in mouse models of infectious diseases.

Background: The potential release of the agent of smallpox, variola virus, as a biological weapon highlighted the need for a vaccine for protection of military personnel and first line responders from infection. The safety of the FDA-approved smallpox vaccines (ACAM2000; live attenuated vaccine for scarification), remains a concern due to increased risk of causing progressive vaccinia (PV) in immune-compromised individuals as well as in individuals with atopic dermatitis/eczema. Traditionally, the efficacy of antiviral therapies for treatments of smallpox vaccine-associated severe side effects such as PV is tested in vaccinia virus (VACV) infected mice by assessing weight loss and viral loads in isolated skin lesions and internal organs, and by measuring the size of the lesion at the site of scarification.

Methods: We developed a new animal model of PV in athymic nude mice (complete absence of T cells). Mice are infected with 105 pfu of recombinant IHD-J-Luc VACV expressing luciferase via scarification at the base of the tail. To mimic immune compromised humans with some immune function, nude mice were partially reconstituted with small number of T cells (10,000 T cell/mouse) one day before challenge. Following infection, viral replication and in-host dissemination is monitored using bioluminescence imaging of live animals. Viral loads are quantified by calculating Areas Under the flux Curve (AUC) for individual mice and are used to determine significance between treatment groups.

Results and Conclusion: Using daily bioimaging of infected mice, we detected viral replication at the scarification site and virus dissemination to internal organs before the appearance of visible lesions. A single dose of human monoclonal antibodies (mAbs) against B5 (EEV membrane protein) administered 24 hours post challenge extended survival of nude mice compared with PBS-treatment by delaying dissemination of the virus from the site of scarification to internal organs (spleen, liver, axillary and inguinal lymph nodes). However, anti-B5 Mab treatment did not reduce viral replication at the scarification site, where virus persisted until the mice succumbed. In contrast, 100% of nude mice partially reconstituted with normal T cells and treated with a-B5 mAbs post-challenge survived infection. Furthermore, all anti-B5 treated T cell reconstituted nude mice cleared the virus from internal organs and from the scarification site, resulting in complete healing of scarification site. Using bioimaging we showed for the first time that in a mouse PV model, VACV undergoes systemic dissemination within 2 days post infection even before lesions are visible at the site of scarification. Passive immunotherapies alone can delay systemic dissemination. Importantly, even low number of transferred T cells can play a crucial role in protecting animals from progression of PV under the umbrella of a potent anti-vaccinia Mab treatment.

References:


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Fusion of Dendritic Cell-Targeting Chemokine MIP3α to Melanoma Antigen Gp100 Significantly Enhances Survival Compared to Antigen-Only Therapeutic DNA Vaccination in Mouse Melanoma Model System

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Objective: Explain that in the context of an anti-tumor therapeutic DNA vaccine, chemokine-fusion vaccines enhance anti-tumor immunity and mouse survival compared to antigen-only vaccines.

Background: The current study demonstrates that a therapeutic vaccination regimen with a DNA vaccine encoding the chemokine MIP-3α fused to melanoma antigen gp100 reduces tumor burden, enhances immunogenicity, and prolongs survival as compared to mock and antigen-only vaccinations in the B16F10 melanoma mouse model. Antigen-only vaccine is defined as gp100 fused to a mutated and non-functional MIP-3α. Previous published work with this vaccine platform has indicated the MIP-3α component targets nascent peptides to immature dendritic cells leading to cell maturation, antigen processing by class I and class II MHC pathways, and antigen cross-presentation to T cells. It has further been shown in this tumor system that prophylactic vaccination with the DNA construct delayed tumor growth.

Methods: This study utilized a standardized mouse model system of melanoma, where a lethal dose of syngeneic B16F10 melanoma cells is injected subcutaneously into the flank of a female 4-6 week old C57Bl/6 mouse. DNA vaccinations are given by intramuscular injection followed by electroporation in the tibialis muscle. Vaccinations are given in series of three: prophylactic at two week intervals prior to tumor challenge and therapeutic at one week intervals starting day three post tumor challenge. Tumors are tracked over time by surface area estimations from caliper measurements, and endpoints include a tumor dimension surpassing 2 cm, significant necrosis, inhibition of movement/feeding, and death. Immune parameters tested by Elispots, intracellular IFN-γ staining of gp100-stimulated T cells, flow cytometry, and In-Cell ELISA assays. To test systemic immune parameters, blood and splenocytes were utilized, and to analyze intratumoral immunity, lymphocyte-enriched tumor homogenate was utilized. Statistical significance threshold set at α < 0.05, with tests noted in parentheses.

Results and Conclusion: First, this study confirmed previous results by finding a significant decrease in tumor burden (anova) and increase in survival (log-rank) of MIP-3α-Gp100 prophylactic vaccination compared to mock. The development of significant cell-mediated and humoral immune responses were documented for the first time in this system by flow cytometry and ELISA assays (t-test). Secondly, with a novel therapeutic protocol, we demonstrated that MIP-3α-Gp100 vaccine significantly reduces tumor burden at critical time points (anova), delays tumor growth over time (mixed effects model), and increases survival compared to mock vaccine and to antigen-only vaccine (log-rank). All parameters tested between mock and antigen-only vaccinations were not significant. This MIP-3α dependent vaccine effect has been found to positively correlate with the percentage and tumor-size normalized numbers of CD8+ T cells reactive to vaccine peptide (t-test). In conclusion, efficient targeting of antigen to immature dendritic cells with a chemokine fusion vaccine has shown to be superior to antigen-alone gp100 vaccination by measures of tumor growth, mouse survival, and immunological parameters in both prophylactic and therapeutic schedules. This vaccine protocol offers an improved approach to the DNA vaccines previously unsuccessful in the clinic and a potential alternative approach to the ex vivo dendritic cell antigen loading protocols currently undergoing clinical investigation. Future work will focus on therapy optimization, especially in the contexts of neoantigens, adjuvants, and delivery methods.
P40

**Streptococcus pyogenes** Vaccination with Peptide Amphiphile Micelles

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**Objective:** Describe a new modular self-assembled vaccine platform that enhances vaccination against Group A Streptococcus.

**Background:** *Streptococcus pyogenes* (Group A Streptococcus, GAS) frequently elicits diseases that range in severity from mild infections of the pharyngeal mucosa and dermis to life-threatening invasive diseases such as necrotizing fasciitis, impetigo, and toxic shock. Epidemiological studies estimate that each year greater than 500,000 worldwide deaths are attributable to GAS infections, placing it among the top ten leading causes of death from infectious pathogens. In the United States alone, more than $600 million is spent annually treating diseases caused by this organism with no effective preventative method established short of prophylactic antibiotic usage.

**Methods:** Vaccines against GAS remain unavailable despite decade’s worth of research and development. While whole-killed and live-attenuated vaccines have been tremendously effective in preventing pathogenic infections, they are also associated with undesirable side effects. Subunit vaccines that deliver just the peptide antigen of interest have been shown capable of stimulating an immune response. But these peptide antigens are generally weak immunogens on their own and require strong adjuvants (non-specific immunostimulants) to be effective. In order to enhance the immunogenicity of peptide vaccines, new delivery systems must be designed. Peptide amphiphiles are unique biomaterials comprised of peptide-lipid conjugates that undergo self-assembly into micelles in water and have been shown capable of delivering biologically active peptides for a variety of applications. Therefore, peptide amphiphile micelles provide a novel platform to improve the host immune response to peptide vaccines.

**Results and Conclusion:** The J8 peptide is a 29 amino acid, conformationally dependent B cell epitope that has been shown to generate an opsonophagocytic, high titer antibody response in mice. J8 was covalently tethered to a di-palmitic acid tail (J8-diC16) and fabricated into peptide amphiphile micelles in PBS. When delivered to mice subcutaneously, J8-diC16 was found to induce J8-specific high antibody titers greater than soluble J8 delivered with commercially available adjuvants. To further enhance the antibody response, mixed micelles comprised of J8-diC16 and amphiphilic adjuvants were synthesized. Mixed micelles induced a strong immune response after a single vaccination and higher titers than all other formulations. It was also discovered that micelles are capable of activating dendritic cells. The research presented in this poster demonstrates the promise peptide amphiphile micelles have in improving the field of vaccine engineering.

**Reference:**

Self-Assembled Immune Signals as a Platform for T Cell Vaccination

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**Objective:** Explain how to employ clinical relevant peptides (e.g., cancer peptides such as trp 2 and hgp 100) into the vaccine platform for treating specific diseases such as melanoma.

**Background:** While nanoparticles laden with antigens and adjuvants have demonstrated great potential in developing novel vaccines for addressing challenges facing infectious diseases, the rational design of these vaccines is hindered by the complexity of many such systems and the intrinsic inflammatory activity of polymeric carriers such as poly (lactide-co-glycolide). To address this challenge, we assembled polyelectrolyte multilayered films entirely from immune signals (iPEM) in a layer-by-layer fashion onto immunologically-inert gold nanoparticles (AuNP). This platform allows modular control over the combinations and doses of immune signals and could contribute to rationally-designed vaccines that generate programmable responses.

**Methods:** SIINFEKL peptide (SIIN) modified with arginine residues (SIIN*, cationic) were assembled with a polyanionic toll-like receptor 3 (TLR3) agonist adjuvant, polyIC, on AuNPs. Splenic dendritic cells (DCs) were treated with iPEM and assessed by flow cytometry. iPEM interaction with HEK-Blue TLR3 reporter cell line assessed activation pathway. Mice were immunized intradermally with iPEMs to assess antigen-specific CD8+ T cells frequency in peripheral blood and SIIN presentation in lymphatic DCs.

**Results and Conclusion:** iPEM were readily synthesized from polyIC and SIIN*, with cargo loading controlled through layer number. DCs treated with iPEM are activated with surface markers (e.g., CD40, CD80 and CD86). HEK-Blue TLR3 cell line treated with iPEM, but not other vaccinations, show the specific activation of TLR3 pathway. DCs present SIIN but no other control peptide in their MHC-I complex. Mice injected with iPEM have a higher frequency of SIIN-specific CD8+ T cells and a higher display of SIIN in lymphatic DCs than other treatments. iPEMs activate DCs and elicit antigen specific immune responses from T cells in vitro and in vivo. Future studies are being performed with clinically-relevant disease models for developing immune responses against specific diseases.

**References:**

Madin Darby Canine Kidney Cell Single-Cell Clones Have an Unstable Non-Tumorigenic Phenotype

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**Objectives:** Develop an understanding that the tumorigenic phenotype of the immortalized cell line, Madin Darby canine kidney (MDCK) cells, is complex. Recognize that epigenetic processes are likely involved in the manifestation of the tumorigenic phenotype of MDCK cells.

**Background:** Madin Darby canine kidney (MDCK) cells are a heterogeneous population of polarized epithelial cells that are used extensively in influenza virus research and for isolation of candidate influenza virus vaccine strains. For several reasons, including its tumorigenic phenotype, viruses isolated in MDCK cells cannot be used as vaccine seed viruses. Understanding the tumorigenic phenotype of MDCK cells may assist in determining whether concerns with its use in vaccine manufacture are warranted. Since MDCK cells are a heterogeneous population, we first sought to determine whether all of the populations comprising the MDCK cell line were equally tumorigenic. To address this question, we isolated subpopulations of MDCK cells and characterized their phenotypes.
**Methods:** MDCK cell single-cell clones were isolated by limiting dilution, subcultured for >90 passages, and the cell morphology, tumorigenicity, and the expression profiles of proteins associated with physiological processes involved in tumorigenicity assessed at early passage (p17), mid-passage (p70), and high passage (101). Morphology was monitored by light microscopy. Tumorigenicity was assessed in newborn athymic nude mice inoculated subcutaneously with 1 x 107 cells in 0.1 mL PBS. Protein expression analysis was done using an automated capillary, size-based electrophoretic immunoassay.

**Results and Conclusion:** Of 13 single-cell clones isolated, 4 representative clones were chosen for further passage and characterization. By microscopic examination, one of the 4 clones exhibited a slight change in morphology, becoming more epithelial over passage. Protein expression analysis showed differential expression of cell-adhesion molecules and tight-junction proteins among the clones over passage. While all clones were non-tumorigenic at early passage, 3 out of the 4 clones induced scoliosis in newborn nude mice (similar to the parental MDCK cells) at mid-passage, and at high passage all clones induced scoliosis and 3 of the 4 clones had become tumorigenic. The tumorigenic clones differed in their efficiency of tumor formation and in their tumor latency. The non-tumorigenic phenotype of MDCK single-cell clones changes over passage in culture. The differences between the clones may indicate that each is a distinct population within the parental line, or that each represents cells at different stages along the pathway to a tumorigenic phenotype. That the single-cell clones acquire characteristics (invasion, tumorigenicity) associated with epithelial-to-mesenchymal transition (EMT), but do not change morphology may suggest that the clones undergo a partial EMT.

**References:**

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**P43**

**Biophysical Characterization of an E. coli Expressed CRM197 Conjugate Vaccine Carrier Protein**

**A. Lees**

1-2

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**Objective:** Explain the use of CRM197 as a carrier protein and the biophysical characterization of the first CRM197 expressed as a soluble protein at high yields in E. coli.

**Background:** CRM197 is genetically detoxified diphtheria toxin and is widely used as a carrier protein in conjugate vaccines, including Prevnar® and Menveo® for prevention of diseases caused by Streptococcus pneumoniae and Neisseria meningitidis as well as in other licensed and experimental vaccines. The CRM197 is a significant portion of the manufacturing cost of many conjugate vaccines. We have developed a system to express soluble, properly folded CRM197 in E. coli as a low cost alternative to CRM197 produced in Corynebacterium diphtheriae (“native” CRM) or Pseudomonas fluorescens (“Pfenex” CRM).

**Methods:** Here we describe some of the biophysical properties of our E. coli expressed CRM and show similarity to either published or experimentally obtained data for native and Pfenex CRM. We provide equivalency data for composition and sequence (amino acid analysis and peptide mapping), stability (differential scanning calorimetry), molecular weight (multi-angle light scattering, and mass spectrometry), structure (circular dichroism, intrinsic fluorescence), folding (receptor binding ELISA and isothermal calorimetry). We also present data showing the stability of concentrated E. coli expressed CRM solutions as a function of pH.

**Results and Conclusion:** CRM197 has been expressed in the E. coli cytoplasm at high levels as a native, properly folded single chain protein, without purification tag. Our biophysical characterization shows that it is similar to native CRM. We note that E. coli CRM, like native CRM but unlike Pfenex CRM, can be concentrated at neutral pH without the use of additives. This work supports the use of our E. coli expressed CRM as a suitable and low cost substitute for CRM197 produced in C. diphtheriae.
Knowledge, Attitudes, Beliefs, and Behaviors of College Students and Staff during a Meningococcal B Outbreak Vaccination Program: A Canadian Immunization Research Network (CIRN) Study


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Objective: List the factors that affect the willingness to receive the meningococcal B vaccine during an outbreak at a university.

Background: In February, 2015, an outbreak of Neisseria meningitidis type B was identified at a Nova Scotia university (~3500 students) and a mass Public Health-delivered vaccination program was implemented with the 4CMenB vaccine. Using an online survey, we explored the knowledge, attitudes, beliefs, and behaviors of members of the university community in relation to the disease, the vaccine, and the vaccination program.

Methods: All students, faculty, and staff eligible for the vaccination program were invited by email to participate in an anonymous, 71 item survey comprising 10 demographic, 1 awareness, 4 behavior, 7 knowledge, and 49 attitude and belief questions. The survey was distributed after completion of the first-dose clinics and reminders sent after completion of the second-dose clinics. Point estimates for each item were analyzed. Items significant at the p < 0.05 in the univariate analysis were entered into the multivariate analysis.

Results and Conclusion: A total of 404 individuals responded to the survey; 75.8% of respondents who provided gender information were female. 306 (75.7%) respondents were students (response rate approximately 9% of the student body), with equal distribution from first to fourth year (20.6%-24.1% of those who provided their year of study); 9.8% were graduate students. 60.8% of respondents were science affiliated majors. Knowledge about meningococcal disease and the 4CMenB vaccine were generally high; 70.8%-96.8% correct responses were received on each knowledge question except for a question exploring the different serotypes of meningococci (49.0%). There were no significant differences between students and faculty or staff members in the responses to the knowledge questions. Being immunized or intending to be immunized was significantly (p < 0.05) associated with gender (78% female vs 22% male) and higher knowledge scores (90.8% ≥4 vs. 9.2% < 4 correct answers). In the univariate analysis, positive attitudes about immunization, concern about the infection, a sense of community responsibility and trust in public health advice also correlated with being vaccinated or intending to be vaccinated (p < 0.05). A family physicians’ recommendation did not play a significant role in the decision whether or not to be immunized. A successful mass vaccination program in a Nova Scotia University (vaccine uptake of 84.8% for dose 1 and 70% for dose 2) was associated with high levels of student knowledge, positive attitudes towards vaccination, and positive attitudes towards public health recommendations.

References:
Objective: Evaluate the effect of e-Health technology for students on a college campus.

Background: According to the 2012 National Healthcare Disparities Report, influenza and pneumonia combined effect 25 million people annually, 8.1% of the population, making them the ninth leading cause of death in the United States. Poor vaccination rates can have tragic results, leading to approximately 36,000 yearly deaths. CDC recommends an annual influenza vaccine for all people over the age of 6 months. The current vaccination rate for US adults is 26%, while the government’s Healthy People 2020 goal is 70%. The current vaccination rate of college students is 40%, while the American College Healthy Campus 2020 goal is 50%. Busy college students often do not seek healthcare advice when they feel healthy and have no perceived self-risk. Campus vaccination rate is a disappointingly low at 15%. Influenza spreads across college campuses nationwide, and students are more likely to catch influenza illness because of risks inherent in college life.

Methods: At a suburban, co-ed, undergraduate liberal arts college, with a population of 1,227 and a cell phone ownership rate of 91%, the students are immunized against the flu at a lower rate (15%) than the national campus average (40%). This is also lower than the rate for all young adults throughout the nation (25%). This suboptimal vaccination rate puts the campus community at risk for influenza outbreak and the possibility of serious health impediments. This public health problem was addressed to avoid campus wide outbreak of influenza and its complications, including death.

Results and Conclusion: This project’s successful use of e-Health technology with text messages linked to health portal technology, along with the knowledge of Integrated Theory of Health Behavior Change (ITHBC), increased influenza vaccination rates on campus. This project is sustainable and easily reproducible. Use of this theoretical ITHBC framework helped to support the careful assessment, planning, and education of students on campus in order to develop the foundation for a lasting acceptance of an annual influenza vaccine. This project supports the use of e-Health technology as an effective method to increase students’ influenza vaccine rate. Current research supported the project’s method to prompt students to vaccinate, and the survey questionnaire results aligned with the present public health evidence based knowledge. The top reasons that influenced students to be vaccinated included to stay healthy and avoid flu illness, family recommendation, health provider recommendation, cost covered by insurance and the health information on the HaverHealth portal. However, public health “flumythbuster” education will need to continue on campus. This will help to convince the refusers and reinforce the facts that the influenza vaccine is the most scientifically safe and effective method to prevent illness and that college students are at risk due to inherent living conditions. The comparison of 2015 to 2014 data showed a remarkable increase in acceptance of influenza vaccine (2.5 times). The vaccination administration rate at Student Health Services increased from 7.5% in 2014 to 20.5% in 2015, which is notable. In the future, e-Health technology with text messages should be used to educate students on the risks and benefits of vaccination, in order to increase acceptance of influenza vaccine.

References:
Developing a Synthetic DNA Vaccine for an Emerging Pathogen - Middle East Respiratory Syndrome


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Objective: Describe the efficacy of the synthetic DNA vaccine platform for Middle East Respiratory Syndrome.

Background: Middle East Respiratory Syndrome (MERS) was first reported in 2012 in Saudi Arabia when a patient died from severe respiratory disease caused by a novel betacorona virus, MERS-CoV. Through November 2015, there have been 1,618 confirmed global cases of MERS-CoV infection and 579 deaths reported to the World Health Organization (WHO). Currently, no vaccine or specific treatment is available and patients are treated with supportive care based on their clinical condition. While most MERS cases occur in and around Saudi Arabia, the recent outbreak in Korea highlights the potential for this disease to spread beyond the immediate region. A vaccine is needed to prevent future disease caused by MERS-CoV.

Methods: A synthetic DNA MERS vaccine was generated using a consensus sequence of the MERS spike protein. Mice, dromedary camels, and non-human primates (NHP) were immunized with MERS-vaccine by intramuscular injection followed by electroporation. Cellular immune responses were measured by flow cytometry and IFNγ ELISpot. Humoral immune responses were measured by ELISA and neutralizing antibody (nAb) assay. Following immunization, NHPs were challenged with infectious MERS-CoV (EMC/2012) and monitored for signs of infection by clinical scoring and examinations. Viral load was measured by qRT-PCR and tissue sections were stained with H&E.

Results and Conclusion: Immunization of mice with MERS-vaccine induced strong humoral and cellular responses. Mice produced strong binding antibody (bAb) titers and nAb titers. A strong, polyfunctional, CD4 and CD8 T cell response was detected against multiple epitopes across the MERS spike protein. Immunization of dromedary camels induced the production of MERS spike specific antibodies and nAbs. Immunization of NHPs induced strong bAb titers and nAb titers and a strong CD4 and CD8 T cell response. NHPs immunized with multiple vaccination regimens were also protected from signs of disease upon challenge with infectious MERS-CoV and showed a greater than three log reduction in viral load after challenge compared to unvaccinated animals. A consensus DNA MERS-vaccine was able to generate both a strong T cell and neutralizing antibody response in multiple animal models, including camels, a natural host for MERS-CoV and a probable source of human infection. MERS-vaccine was also able to protect NHPs from an infectious MERS-CoV challenge. These results demonstrate the promise of this consensus DNA MERS-vaccine as a candidate for vaccine development.

References:

Effect of Adjuvant Formulation on the Immunogenicity and Protective Efficacy of *Salmonella Enteritidis* Core-OPS (COPS) Conjugates with Flagellin in Infant and Adult Mice

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**Objective:** Explain whether *S. Enteritidis* COPS:FliC is immunogenic and effective in infant mice.

**Background:** Non-typhoidal Salmonella (NTS) serovars Enteritidis and Typhimurium are major causes of invasive disease in children in sub-Saharan Africa.\(^1\) NTS COPS and flagellar proteins are virulence factors and protective antigens in animal models. Isolated NTS COPS are poorly immunogenic in animals; however, covalent coupling to proteins overcomes these limitations. Glycoconjugates of *S. Enteritidis* COPS with the homologous serovar flagellin protein (FliC) induced measurable anti-COPS and anti-flagellin IgG and provided protection against fatal *S. Enteritidis* challenge in adult mice.\(^2\) There have been no preclinical studies with NTS COPS conjugates in infants, the target population for a NTS vaccine.

**Methods:** Infant (2 week-old) or adult (6 week-old) CD-1 mice were immunized three times at two week intervals with *S. Enteritidis* COPS:FliC alone or formulated with aluminum hydroxide (Alhydrogel™), double mutant heat Labile Toxin (dmLT) from *E. coli*, or monophosphoryl lipid A (MPLA). Serum samples were collected at baseline and fourteen days after each immunization. Four weeks after the final immunization, mice were challenged intraperitoneally with a fatal dose of *S. Enteritidis* R11 (Malian invasive isolate). Serum samples were assessed for anti-COPS and anti-FliC IgG titers. Geometric mean titers (GMTs) were compared by Mann-Whitney (2-tailed, \(\alpha=0.05\)) and percent survival by Fisher’s exact test (2-tailed, \(\alpha=0.05\)).

**Results and Conclusion:** COPS:FliC immunization induced robust anti-FliC IgG titers in adult and infant mice. Anti-FliC IgG GMTs were improved in adult mice after formulation with any of the selected adjuvants (\(P<0.005\)); however only formulations containing dmLT or MPLA boosted these responses in infant mice (\(P<0.01\)). Anti-COPS IgG GMTs were lower compared to anti-FliC GMTs. We found unexpectedly that improvement of anti-COPS IgG titers by adjuvant could only be achieved in adult mice after formulation with MPLA (\(P<0.01\)). Adult and infant mice immunized with COPS:FliC formulations were significantly protected against fatal challenge (\(P<0.001\)); however, formulation with dmLT diminished the level of protection in infant mice (35% vs. 76%) (\(P<0.05\)). *S. Enteritidis* COPS:FliC glycoconjugates were immunogenic in both adult and infant mice and imparted protection against lethal challenge with a relevant sub-Saharan clinical *S. Enteritidis* isolate. A differential adjuvant effect was found for the protein and polysaccharide components, wherein improvement of the anti-protein immune response could be achieved by all adjuvants; however, enhancement of anti-COPS titers was only found in adult mice after formulation with MPLA.

**References:**

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The iVAX Toolkit: A Powerful Suite of in Silico Vaccine Design and Analysis Algorithms


EpiVax, Inc., Providence, RI

**Objective:** Illustrate the power of in silico epitope discovery and optimization tools for the purpose of vaccine design and evaluation.
**Background:** Key issues facing vaccinologists today include prediction of immune response to emerging infectious diseases and cancers and design of novel and next generation vaccines. To address these challenges, we have leveraged computing power, the availability of terabytes of genomic data, and advanced immunoinformatics tools to harness T cell immunity for production of safe and effective vaccines.

**Methods:** Highly immunogenic peptides conserved across multiple strains of input pathogen sequences are identified using the Conservatrix, EpiMatrix, and EpiAssembler algorithms. Potential vaccine candidate epitopes can be aggregated into a string-of-beads design with the VaccineCAD algorithm, simultaneously minimizing deleterious junctional epitopes that may be created in the linking process. JanusMatrix, an enhanced homology analysis tool examining pathogen/host sequence similarity at the TCR interface of any given peptide, predicts potentially cross-reactive epitopes, allowing candidate sequences with potential host cross-reactivity to be preferentially excluded from vaccine constructs.

**Results and Conclusion:** Most recently, low immunogenicity H7N9 influenza antigens with high human cross-conservation were engineered to include epitopes more highly cross-conserved with circulating influenza strains, resulting in a 5-fold increase in post-vaccination antibody titers compared to wild type protein. The JanusMatrix tool also successfully identified the cross-reactive epitope between the MAGE A3 immunotherapeutic and human titin implicated in two fatalities among melanoma and myeloma clinical trial participants. Recent emergence of H7N9 influenza illustrates the difficulties associated with ‘standard’ approaches to vaccine development, while modern cancer vaccine research has underscored the danger of auto-reactive vaccines and immunotherapeutics. These studies provide an opportunity to apply immunoinformatics tools to develop safe and effective responses to these challenges. The iVAX toolkit is poised to accelerate the development of targeted, safe and efficacious vaccines, which will address important global health and biodefense challenges.²³ Collaborations accepted and encouraged.

**References:**

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**P49 Immunoinformatic Approaches to Identifying Novel *Ehrlichia chaffeensis* Vaccine Candidates**

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**Background:** *Ehrlichia chaffeensis* is a gram-negative, obligately intracellular bacterium that selectively infects mononuclear phagocytes and causes human monocytotropic ehrlichiosis (HME), emerging life-threatening tick-transmitted human zoonoses. Currently there are no vaccines available and little is known about the pathogen-and host-specific interactions and mechanisms contributing to disease pathogenesis and immune evasion. Recent investigations have led to the identification of some immunoreactive proteins of *E. chaffeensis*, including outer membrane proteins, ankyrin repeat proteins and tandem repeat protein (TRP) effectors, representing only 5-10% of the entire repertoire of antigenic proteins. Hence, many proteins essential for complete vaccine efficacy remain undefined.¹

**Methods:** In silico antigen prediction was carried out using ANTIGENpro², to identify the antigenic/protective proteins, which were cloned and expressed in an in vitro transcription/translation system and subjected to immunoscreening with convalescent sera from HME patients. A second level ranking of antigenic proteins was based on overall immunoreactivity score, and expression level in vivo based on transcriptome/proteome data in order to assign priority to highly immunoreactive/expressed proteins. The selected top antigenic proteins are expressed in bulk using optimized vector and bacterial expression systems, and refolding strategies to maintain conformational epitopes.
Results and Conclusion: Preliminary genome-wide scan using a sequence-based prediction model, ANTIGENpro, led to the identification of a large group of antigenic proteins including known immunoprotective proteins of *E. chaffeensis*. Data on transcriptome and proteome analysis of *E. chaffeensis* in tick and mammalian cells was utilized to create a prioritized list of proteins. The analysis revealed that a group of hypothetical protein genes are the most differentially and highly expressed genes in Ehrlichia between the two hosts suggesting that many novel antigenic and potentially protective proteins have unknown function. The top 100 predicted antigenic proteins were expressed in vitro and examined for immunoreactivity by ELISA. Top 25 proteins with immunoreactivity greater than a characterized immunogenic protein (TRP47) were identified which included novel candidates. These select candidates are currently being expressed, purified and refolded (as required) for further studies. A high throughput genome-wide antigen identification strategy utilizing immunoinformatics, transcriptomics and proteomics approaches was successfully applied to shortlist novel protective antigens of *E. chaffeensis*. The top antigenic proteins will be further tested in animal models for protective efficacy against homologous challenge to create a final list of vaccine candidates.

References:

P50

A Recombinant Subunit Vaccine for Bovine RSV and *Histophilus somni* Protects Calves against Dual Pathogen Challenge

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Objective: Explain the synergy between bovine respiratory syncytial virus and *Histophilus somni* in causation of bovine respiratory disease and how recombinant subunits from each of these pathogens can be used to evoke protective immunity in a vaccine.

Background: Bovine respiratory syncytial virus (BRSV) and *Histophilus somni* synergize to cause bovine respiratory tract disease. Vaccines containing formalin inactivated (FI) BRSV in alum adjuvanat have been shown to elicit IgE and to cause disease enhancement; similarly *H. somni* bacterins have been associated with an IgE response. We hypothesized that a subunit vaccine consisting of the nucleoprotein (NP) from BRSV and the recombinant antigen IbpA DR2 (a surface antigen of *H. somni* with the toxic motif DR2) in Quil A adjuvant would elicit protection without enhancement. Both of these antigens have previously been shown separately to induce protection from the individual pathogens.

Methods: Three groups of 6 week old six Holstein bull calves were vaccinated with either: FI/Somnivac (a commercial *H. somni* bacterin) in alum, recombinant yeast expressed NP & recombinant IbpA DR2 in Quil A, or Quil A adjuvant alone. Vaccines were given two times at a 3 week interval and calves were challenged with BRSV by aerosol one week after the final vaccine. On day 6 following viral challenge calves received a *H. somni* challenge by the intracheal route. Clinical scores were collected for 23 days after virus challenge. At seven time points serum IgG1, IgG2, and IgE levels were measured by ELISA against both whole pathogens and subunits. Bronchoalveolar lavage was performed at three time points and lung lavage fluid was similarly assayed for antibody levels. T cell subsets in peripheral blood were evaluated by flow cytometry. At day 23 calves were euthanized and lung gross and histopathology was performed.

Results and Conclusion: Clinical scores were significantly greater for the FI/Somnivac group; and both clinical and lung pathology scores for the NP & IbpA DR2 group were lowest. FI/Somnivac induced IgE to *H. somni* and to BRSV but not to NP or IbpA DR2 antigens. The NP& IbpA DR2 vaccine did not induce an antibody response to BRSV, but did induce an IgG response to the subunits. There were no significant group differences between CD4⁺ IL-4⁺, CD4⁺ IFN gamma⁺, or CD4⁺CD25⁺fox P3⁺ (regulatory T) cells. Infection with BRSV showed a significant (day) effect on these cell populations. CD8⁺ cells did not differ between groups but there was a significant effect of vaccination on these cell populations. In conclusion, a subunit vaccine consisting of recombinant BRSV NP and
**H. somni** IbpA DR2 with Quil A adjuvant provides protection without adverse effects and is a good candidate for protection of calves against co-infection with these pathogens.

References:

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**P51**

**DNA Vaccination Encoding Beta Toxin of Clostridium perfringens Combined with Heterologous Booster Elicits Protective Immune Response in Mice**

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**Objectives:** Evaluate the efficacy of DNA-based vaccine in combination with heterologous booster to enhance humoral and cell mediated immune responses. Assess the neutralization potential of the antisera against beta toxin toxicity.

**Background:** Beta toxin, a major toxin produced by *Clostridium perfringens* type B and C strains, is responsible for necrotic entritis and enterotoxemia in agriculturally important animals and causes major economic losses to the agricultural industry.\(^1\) Due to rapid progression of the diseases, post-infection therapeutic approaches are of minimal help and prophylactic measures are the only alternate to prevent the infection. Currently used toxoid preparations are often associated with antigenic load and non-focussed immune responses. Therefore, a vaccine preparation able to generate long-lasting focused immune response is highly desirable.

**Methods:** PCR-amplified cpb gene fragment (NCBI Accession No. Q46308) was cloned into pDisplay mammalian expression vector for secretory expression, to develop a DNA-based vaccine against beta toxin. Secretory expression of beta toxin from the construct was analyzed by Western blot analysis of culture supernatant and cell lysate of CHO-K1 cells transfected with the construct. Potency of the cpb gene based DNA vaccine in mice was evaluated using both homologous (DNA-DNA) and heterologous prime boost (DNA-rCPB booster) strategies.

**Results and Conclusion:** BALB/c mice immunized using heterologous prime-boosting strategy showed approximately 10 fold- beta toxin specific antibody titers in comparison to homologous prime boosting strategy. Immunization with the DNA construct encoding beta toxin and boosted with recombinant CPB (rCPB) generated antibodies highly specific to rCPB. Splenocyte proliferation assay showed that immunization using prime-boosting strategy could generate T cell memory and Th1 biased-immune response. Immunized mice were protected against the toxin challenge. The antisera was able to neutralize the toxicity of the beta toxin in vitro. Immunization of mice with the DNA construct expressing CPB conferred 100% protection against beta toxin challenge. Our findings clearly demonstrate the vaccine potential of a DNA-based vaccine against the beta toxin of *C. perfringens* using heterologous prime-boosting strategy, capable of generating protective immune response.

**References:**
Detection of Hepatitis B Virus Immune Escape Mutants among Asymptomatic Population Group in Southwestern Nigeria
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Objective: Explain the diversity of HBV and its implication on the current vaccine strategy.

Background: Hepatitis B virus (HBV) infection is vaccine preventable. Circulation of immune escape mutants (IEMs) has been documented. This poses a risk on the continual success of HBV prevention and control. Therefore this study was designed to determine the possible circulation of IEM among asymptomatic dwellers in southwestern Nigeria.

Methods: Blood samples collected from consenting 133 males and 305 female participants in Ibadan were tested for HBsAg, HBeAg, HBcIgM, HBcTotal and HBsAb by ELISA technique. Samples positive for HBsAg were further analyzed for HBVDNA by amplifying and sequencing the S gene. Isolates were genotyped and subtyped based on amino acid residues at position 122, 127, 134, 160 of the S gene.

Results and Conclusion: Of the 438 subjects tested 31 (7.1%) were positive for HBsAg, 2(6.5%) of which were HBeAg positive. Ninety-nine (22.8%) had detectable HBsAb, 3(0.7%) were positive for HBcIgM and 195 (44.5%) were HBcTotal positive. HBVDNA was amplified and sequenced in 27 out of 31 and 4 could not be amplified due to low titres. After sequencing, 9(33.3%) were not exploitable due to the presence of multiple peaks. Of the 18 exploitable isolates, only 15 showed significant similarity to HBV S-gene. Eleven of the 15 isolates were subtyped as ayw4 while others could not due to substitution at s122p. Phylogram showed that the 11 isolates were genotype E. Two of the 4 isolates with R122Q/P substitutions also belonged to genotype E while the other 2 which were >11% divergent from the reference genotype E sequence clustered with an isolate previously described as an Immune Escape Mutant. This study identified high endemicity of HBV infection, presence of markers of infection even in non-detectable HBsAg levels and circulation of genotype E ayw4 and vaccine mutants in southwestern Nigeria. It therefore emphasizes the risk of development of an indigenous infected population that may not be protected by the current vaccine.

References:

Preparing for an Outbreak of Ebola Virus Disease in Nigeria: Barriers and Safety Concerns of the Use of the Ring Vaccination Design
O. Onigbogi1, O. Ojo2
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Objective: Outline the challenges that would most likely confront future Ebola vaccine disease trials.

Background: Studies have shown that available experimental Ebola vaccines confer some degree of protection against infection in people who are at high risk of contracting the Ebola virus. This study was conducted to assess the willingness to participate (WTP) as subjects in Ebola vaccine trials, using the ring vaccination design among adult artisans in Lagos, Nigeria.

Methods: Self-administered questionnaires were completed by 277 respondents (121 males and 156 females) with age ranging from 18 to 59 years. Questions were in English language. SPSS version 15 data editor was used to analyze data. Univariate odds ratios and 95% confidence intervals (95 % CI) were used to evaluate the correlates of WTP among the participants.

Results and Conclusion: A total of 65 (24%) of the respondents reported that they will be willing to participate in experimental Ebola vaccine trials. Higher willingness was associated with good knowledge of Ebola Virus Disease (OR = 1.33, 95% CI: 1.18–1.53), higher income bracket (OR = 1.45, 95% CI: 1.15–1.62), higher levels of
education (OR = 1.37, 95% CI: 1.24–1.55) and monetary incentives (OR = 1.29, 95% CI: 1.12–1.42). Decreased WTP was associated with concerns about physical harm (OR = 0.52, 95% CI: 0.31–0.54), social stigmatization (OR = 0.51, 95% CI: 0.42–0.88) and concern about infection with the virus (OR = 0.71, 95% CI: 0.46–0.83). The low level of WTP recorded indicates that much work still needs to be done in the area of educating the general populace about safety in vaccine trials. Incentives for would-be subjects should also be a part of the planning to encourage greater participation in these trials.

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NFID Educational Initiatives & Online Resources

The following websites provide tools and resources about vaccine-preventable diseases from NFID and partners for healthcare professionals, consumers, and media.

[Image] www.preventchildhoodinfluenza.org

- Are You a Flu Fighter? Free Downloadable Coloring Book in English and Spanish
- Keep Flu Out of School Materials, including sample lesson plans for teachers
- Ready to use templates for reminder postcards and emails, waiting room posters, and sample voicemail reminder scripts

[Image] www.adolescentvaccination.org

- Adolescent Vaccination Call to Action: Protecting Adolescents Now and Into the Future
- HPV Resource Center and Call to Action: HPV Vaccination as a Public Health Priority
- Meningococcal Vaccination: Improving Rates in Adolescents
- Ready to use templates for reminder postcards and emails, and sample voicemail reminder scripts

[Image] www.adultvaccination.org

- Immunization Tracking Forms
- Toolkit for Adult Immunizations & Standing Order Programs
- Vaccines for Adult Patients: Resources for Educating Adult Patients about Vaccines
- Pneumococcal Disease Vaccination Resources including at-a-glance fact sheets for at-risk adults

[Image] www.family-vaccines.org

- Call to Action: Improving Vaccination Rates in Pregnant Women: Timely Intervention – Lasting Benefits
- Easy to find information on current recommendations, news, and interactive tools
- Video: Vaccines for the Entire Family

[Image] www.nfid.org

- General information on vaccines, including:
  - FAQs
  - Immunization resources for the workplace
  - Vaccine Safety
- Image library
- Professional live and online educational activities
- Real-life stories from individuals affected by vaccine-preventable diseases
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NFID is a non-profit 501 (c)(3) organization founded in 1973 and dedicated to educating the public and healthcare professionals about the causes, treatment, and prevention of infectious diseases. NFID achieves its mission by supporting research and training, building coalitions, and honoring scientific and public health achievements.

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