Mechanisms of a Mosquito-based Malaria Transmission Blocking Vaccine

Malaria continues to be a tremendous public health burden worldwide, yet no vaccine or long lasting control strategy has been developed and successfully implemented to curtail the disease. Transmission-blocking vaccines (TBVs) that prevent obligatory sporogonic development of parasites within Anopheles mosquitoes, and thus the subsequent cascade of human infections, are a potential strategy to prevent the spread of malaria. Anopheles gambiae alanyl aminopeptidase (APN1) was recently identified as a highly conserved, putative mosquito midgut ligand for Plasmodium ookinete. Antibodies raised against a 135 amino acid N-terminal fragment (NT135APN1) in rabbits demonstrated cross-species inhibition, preventing development of P. falciparum in An. gambiae and the murine malaria parasite, P. berghei, in An. stephensi in laboratory models. We report here on the immunogenicity and efficacy of APN1 as a TBV antigen in multiple animal models, including immunological aspects of the mechanism of α-APN1 antibodies. Immunization of inbred and outbred mice and non-human primates with NT135APN1 elicited potent transmission-blocking antibody titers against a lab strain of P. falciparum, while rabbit α-APN1 Abs inhibited field isolates of P. falciparum and P. vivax in An. gambiae s.s. and An. dirus A, respectively. Synthetic peptide-based ELISAs and comparative immunoblotting suggest that transmission-blocking activity of α-APN1 antibodies in each of these animal models is conferred by binding at least one of two conserved predicted linear B cell epitopes. Antibodies from mice immunized with peptides corresponding to these epitopes exhibited cross-reactive recognition of recombinant and native APN1 and transmission-blocking assays are underway. Finally, α-APN1 antibodies appear to inhibit Plasmodium transmission by binding ookinete, either directly or indirectly, and not by inhibiting aminopeptidase activity of APN1. These data provide initial proof-of-principle for the plausibility of a mosquito-based pan-malaria TBV.

*1. Jennifer Armistead


Pertussis in California 2005-2010- Epidemiology and Geographic Distribution of Cases and Personal Belief Exemptions

Background: In 2010 the state of California experienced an outbreak of pertussis larger than the state had seen in 63 years with more than 9,100 documented cases. While pertussis exhibits cyclical patterns in the state, the largest peak year previously was in 2005 when 3,185 cases were seen. No year has shown such a dramatic incidence of pertussis since pertussis-containing vaccine introduction in the mid-1940s.

Personal belief exemptions to vaccination in California have also been increasing in recent years. Statewide about 502,286 children entering kindergarten received a PBE in the 2009-10 school year. While that only constitutes about 2% of all California kindergarteners, there are 430 schools in California with more than 10% of their entering students exempting from vaccination and 50 schools with greater than half exempting. While the overall immunization coverage in the state is high, there are many areas where coverage among kindergarteners has fallen dangerously below the 92-93% coverage levels needed for herd immunity against pertussis. Previous studies have identified spatial time clustering between geographic areas of high personal belief exemption to vaccination (PBE) and incidence of pertussis, and it is hypothesized that this is also occurring in California.

Methods: Data on all pertussis cases in the state with onset dates from January 1, 2005 through December 31, 2010 were obtained from the Immunization Branch of the California Department of Public Health and analyzed to produce detailed descriptive epidemiology of this time period, elucidate potential differences between peak and nonpeak years, and describe the epidemiologic characteristics of the 2010 outbreak. Additionally, in order to determine if sophisticated cluster analysis of these data is warranted here, all cases of pertussis were geocoded and aggregated to census tract level and mapped using geographical information systems (GIS) software. Elementary school exemption data were also geocoded and mapped for all school years from 2005-06 through 2009-10. A set of maps overlaying these data were also created to look for potential spatial clustering.

Conclusions: There do not appear to be significant epidemiologic differences in peak versus non-peak years rather changes in the epidemiology of pertussis are occurring over the time period. Some of the most notable changes include increasing cases in children age >6 months to 19 years, and increasing proportion of cases in females versus males with increasing age. There does appear to be geographical clustering of areas of high exemption and areas of high incidence in many areas of the state. More sophisticated analysis should be conducted.

* denotes student posters eligible for the poster competition
GAVI’s Immunization Data Quality Assessment Project – Developing a Toolbox to Evaluate Country Immunization Coverage Estimates

Immunization coverage data is of upmost importance to the GAVI Alliance and its partners. These numbers are essential not only for monitoring the success of country immunization programs, but also for setting new targets, monitoring grants, evaluating country readiness for introduction of new vaccines, stock management and even demand forecasting.

Immunization coverage is estimated several ways, including by the country’s own administrative data system and through national surveys such as the Demographic and Health Surveys. Additionally, a WHO/UNICEF working group produces WHO/UNICEF estimates of national immunization coverage, the WUENICS, annually for each country. However, these various estimates of immunization coverage often differ and many countries have problematic, insufficient or weak data collection systems.

Due to the multifaceted importance of accurate coverage data, GAVI and its partners have used various methods to evaluate country-reported coverage in the past. The Data Quality Audit (DQA) and Data Quality Self-Assessment (DQS) tools were the most widely used methods. Evaluation of these tools and their use over the last decade has identified a need to redesign an assessment procedure that could be both diagnostic and prescriptive—something that would identify problems in reported coverage estimates, discern what system components might be leading to inaccuracies and assist countries in improving their systems overall.

Toward this aim, the GAVI Alliance has assembled a task team of fifteen members from various partner organizations and GAVI countries to develop a new methodology for evaluating country administrative data systems and the immunization coverage estimates they produce. The project is ongoing, but hopes to revolutionize the way GAVI assesses these crucial data and lead to improvement of country data systems over time.

Investigating the Genotypic Distribution of High-Risk Human Papillomavirus among Women in Northern Tanzania in an Effort to Determine Vaccine Efficacy

Background: Persistent infection with an oncogenic strain of high-risk human papillomavirus (HPV) is the initiating event for more than 85% of cervical cancer cases throughout the world. The burden of cervical cancer falls most heavily on the poorest countries in Sub-Equatorial Africa, and the World Health Organization recently reported that Tanzania has the highest incidence of cervical cancer in the world. Tanzania has extremely limited preventive health services, an annual government per capita health expenditure of US$27, and no organized cervical cancer screening program. In 2006, approximately 7,000 women in Tanzania developed cervical cancer, and an estimated 6,500 women died from the disease. In that same year, a HPV quadrivalent (types 6, 11, 16 and 18) vaccine was introduced that is efficacious in the Western world, where 70% of cervical cancer cases can be attributed to oncogenic HPV types 16 and 18. It is unclear, however, if the same strains of high-risk HPV are affecting Tanzania, consequently questioning the efficacy of the quadrivalent vaccine in Tanzania.

Methods: 324 women, aged 30-60, were recruited from villages near Selian Lutheran Hospital in Northern Tanzania. Inclusion criteria included: no prior cervical screening, no prior hysterectomy, no current pregnancy, and no irregular bleeding. Each woman received group informed consent followed by individual informed consent, in their native language of Swahili or Maa. Women who were recruited to the study received a breast exam, GYN exam, Pap test, STD screening and a rapid CareHPV ® test developed by Qiagen. The rapid CareHPV ® test was used to identify and genotype HPV infection among these women, providing information about vaccine efficacy.

Results: 42 of the 324 women (12.8%) were positive for high-risk HPV, but only 7 of these 42 women (16.7%) were positive for HPV oncogenic genotypes 16 and 18. The remaining 35 women (82.3%) were positive for other high-risk HPV strains.

Conclusion: The current quadrivalent vaccine would not be efficacious in Northern Tanzania because of the low reported prevalence of oncogenic HPV types 16 and 18. A larger study is needed to confirm this conclusion.
The Johns Hopkins Vaccine Initiative
Vaccine Day 2011 Poster Session

*5. Cailin Deal

Cailin Deal, Gary Ketner and Andrew Pekosz

The role of the Influenza A Virus M2 protein extracellular domain in virus replication and on the induction of broadly protective antibodies

Influenza vaccines are critical for reducing morbidity and mortality associated with annual influenza epidemics. These vaccines protect primarily by inducing neutralizing antibodies targeting the hemagglutinin (HA) protein. Current influenza vaccines provide good protection from infection with antigenically matched virus strains but provide limited protection when circulating virus strains undergo either antigenic shift or drift. The extracellular domain of the M2 protein has been proposed as a potential universal vaccine target due to its conserved nature and the ability of antibodies that recognize this domain to protect animals from influenza A virus infection. To further investigate M2 ectodomain (M2e) based influenza A virus vaccines, various M2e sequences have been inserted into the hypervariable region 5 (HVR5) of the hexon capsid protein of recombinant adenovirus serotype 5 (Ad5) in order to create a replication competent vaccine that displays M2e sequences on the surface of the virion. Concurrently, the functional significance of the M2e domain is being determined by creating MDCK cell lines stably expressing M2 proteins containing various mutations in the extracellular domain. M2 proteins containing alanine substitutions at residues 2-4, 5-7, 18/20-21 and 22-24 in the M2 ectodomain were able to complement the replication of M2-null viruses, demonstrating that they are not critical for M2 function. Using these approaches, we will identify sequences important for M2e immunogenicity and function, thereby providing important insights into the likelihood of M2 antibodies providing selective pressure for the virus to escape the immune response and to further understand the role that M2 plays in the viral life cycle.

*6. Andrea Feller

Andrea J. Feller, K. Zaman, Kristen Lewis, Ilias Hossain, A.S.G. Faruque, Md. Yunus, and David A. Sack

Severity of Non-rotavirus Acute Gastroenteritis Episodes among Vaccinated and Unvaccinated Children enrolled in a Randomized Clinical Trial with the Pentavalent Rotavirus Vaccine (PRV) in Bangladesh

Rotavirus infection is common among children under two years of age in Bangladesh. Infection with rotavirus is known to cause damage to the mucosal epithelium. We hypothesized that this damage may make children in this setting more susceptible to infection with other enteric pathogens, or may make these infections more severe. Therefore, infants immunized against rotavirus may also be indirectly protected against non-rotavirus diarrhea or may have less severe illness. A randomized clinical trial of the pentavalent rotavirus vaccine (PRV), RotaTeq, was recently conducted in Bangladesh. Data on non-rotavirus episodes of gastroenteritis were collected as part of the trial, and Vesikari severity scores were calculated for these cases. The aim of this study was to determine if infants in Bangladesh vaccinated with PRV had a reduced severity of diarrhea caused by non-rotavirus pathogens compared to children receiving placebo. Among 604 episodes of non-rotavirus gastroenteritis in this cohort, we did not find a difference in the mean Vesikari score between treatment groups, nor was there a difference in the odds of having a severe or very severe episode of diarrhea by treatment group. Because this analysis did not find an indirect benefit of PRV on non-rotavirus diarrhea episodes, we recommend that rotavirus vaccines be used in conjunction with other programs to reduce the burden of diarrheal diseases in these settings.

*7. Dustin Gibson

A systematic review of the literature on the effect of distance of residence from health care facility and immunization coverage

In the midst of the Decade of Vaccines, millions of dollars have been committed to lowering the cost of vaccines and making them more affordable for people living in the lower income countries. However, price reductions alone do not ensure each child will be fully vaccinated. Theoretical frameworks and scientific studies suggest additional factors associated with vaccine receipt. These include caregiver autonomy, vaccine benefit beliefs, and proximity to health care facility, amongst others. Although distance of residence from a health facility or time spent traveling there, does not solely explain a child’s immunization status, understanding and acknowledging its importance is necessary in order to achieve high population immunization coverage levels. We are conducting a systematic review of the published literature and meta-analysis of distance from health facility and its effect on immunization coverage and other forms of health care utilization. Vaccine studies were grouped according to outcome as the following: 1. Full childhood immunization status 2. BCG vaccine at birth and 3. Maternal Tetanus Toxoid immunization. Preliminary results show a strong distance decay effect on full immunization status.

* denotes student posters eligible for the poster competition
*8. Kyla Hayford

Validating measles vaccination coverage estimates using an oral fluid biomarker: Preliminary findings from a population-based study in rural Bangladesh

Vaccination coverage, based on reported or recorded vaccination status from sample surveys and clinic records, is widely used as an indicator of immunization and health systems functioning and progress toward Millennium Development Goal 4. But how well do conventional methods of ascertaining vaccination status actually predict susceptibility in a population? Antibody prevalence surveys using oral fluid samples are a non-invasive, low-cost and safer alternative to blood collection for evaluating population immunity to vaccine-preventable diseases. Our aim is to estimate immunity to measles virus using an oral fluid biomarker and compare it to vaccination cards and maternal recall of measles vaccination. A cross-sectional survey with oral fluid collection was conducted with children ages 12-16 months in Mirzapur, Bangladesh. Oral fluid samples were tested for measles-specific IgG. The questionnaire elicited the child’s vaccination history first based on the mother’s recall and subsequently on the child’s vaccination card. An estimated 1,200 children will provide adequate samples for analysis. Results from the antibody test are assumed to be vaccine-induced because the last measles outbreak in Bangladesh occurred in 2007. Population immunity to measles will be ascertained from oral fluid and compared to vaccination coverage rates calculated from the ‘card plus report’ method and from government clinic records. Individual level analyses will include assessing if maternal recall or card records are adequate predictors of measles immunity and identifying family characteristics associated with discordant results between reported or recorded vaccination history and antibody status. Because many countries are getting closer to eliminating measles, it has become increasingly important to assess if vaccination history is a good predictor of immunity and whether oral fluid biomarkers are a feasible substitute for monitoring immunization performance.

*9. Kevin Hur

Hepatitis B Immunization in the Asian and Latino Communities of Alameda County, California

Background: The purpose of this study is to estimate the prevalence of the hepatitis B virus (HBV) infection and to examine factors related to HBV vaccination among various Asian and Hispanic populations in Alameda County, CA.

Methods: A cross-sectional study was conducted with 792 Asian and Hispanic residents of Alameda County who registered with the Hep B Project, a nonprofit HBV screening program, from June 2009 – February 2011. All participants completed a survey containing sociodemographic questions. Participants were then offered free hepatitis B blood testing. Blood was collected by venipuncture and tested for the hepatitis B surface antigen (HBsAg) and antibody (HBsAb). The 6-month 3-shot vaccination series for hepatitis B was provided for free to participants who did not have the HBsAg and HBsAb. Multivariate regression analysis was conducted to examine the factors associated with completion of a series of vaccinations.

Results: Among the 792 registered participants, the mean age was 47.0 years with a 14.9 SD. 53.4% were female. 84.4% (n=669) of registered participants received a blood test. Ethnicity and living with an HBV carrier significantly affected whether a registered participant followed through with the blood test. Of all the tested participants, 7.9% (n=53) tested HBV positive (HBsAg+, HBsAb-), 46.2% (n=309) were HBV negative but protected (HBsAg-, HBsAb+), and 45.9% (n=307) were susceptible to HBV infection (HBsAg-, HBsAb-). Among those unprotected, about 60% completed the 3-shot vaccine series, 15% received 2 shots, and 6% received 1 shot. About one-fifth of unprotected participants did not receive any vaccinations. Multivariate analysis showed that being Vietnamese (OR=5.53, 95%CI 1.54, 19.85), living in the U.S. > 10 years (OR=2.12, 95% CI 1.13, 3.97), and having at least a college education (OR=2.55, 95% CI 1.28, 5.07) were independent predictors of vaccine completion.

Conclusions: Given the various HBsAg+ prevalence, screening rates, and vaccine completion rates among the different ethnic groups in this study (Chinese, Mongolian, Vietnamese, Hispanic, and Other), it is clear that different approaches in educating, screening, and vaccinating individual ethnic groups for hepatitis B are warranted. Furthermore, this study supports public health vaccination efforts directed towards recently arrived populations that have a high school education or lower.
*10. Erin Lalime
Erin N Lalime, Emad Ellassal, Wen-Hsuan Lin, Diane Griffin and Andrew Pekosz

Influenza A virus infection and replication in primary differentiated epithelial cells derived from Rhesus Macaque upper and lower airway

Nonhuman primates such as rhesus macaques are used as models for influenza A virus pathogenesis as well as vaccine efficacy and safety. In vivo, influenza A virus infects and replicates primarily in respiratory epithelial cells. To investigate the interaction between influenza A virus and the target cell type, we established an in vitro primary differentiated tracheal epithelial cell (TEC) and nasal epithelial cell (NEC) culture system using tissue derived from rhesus macaques. The differentiated cultures supported replication of multiple laboratory and clinical isolates of influenza A virus including the 2009 H1N1 pandemic strain. Not all cells in the cultures are susceptible to influenza A infection. This susceptibility can be correlated in part with the presence or absence of α2,6 or α2,3 linked-sialic acid (SA), both of which were present in the cultures as judged by binding with specific lectins. Altering the receptor binding specificity of the hemagglutinin (HA) protein encoded by A/Udorn/72 (H3N2) resulted in altered virus replication and cell tropism. The virus with α2,6 SA affinity replicated to a higher level and infected ciliated cells more exclusively than viruses encoding HA proteins with mixed receptor recognition or enhanced α2,3 SA recognition. The rhesus macaque TEC and NEC cultures provide a relevant in vitro culture system that can be used with in vivo rhesus macaque studies to focus on epithelial specific responses to influenza A virus infection.

*11. Wendy Lin
Wen-Hsuan Lin, Annie Tsay, Erin N. Lalime, Andrew Pekosz and Diane E. Griffin

Interaction of a Live Attenuated Measles Vaccine with Primary Differentiated Tracheal and Nasal Epithelial Cells Derived from Rhesus Macaques

Measles remains an important cause of childhood mortality worldwide. Sustained high vaccination coverage is the key to preventing measles deaths and may be facilitated by respiratory delivery of the vaccine. Previously, we demonstrated that respiratory delivery of a dry powder live-attenuated measles vaccine (MVDP) was safe and effective in a highly relevant rhesus macaque (RM) model. However, the biology of MV infection of the respiratory tract is largely unknown. To investigate the interaction of MV with respiratory epithelial cells, we established a primary differentiated airway epithelial cell culture system using tracheal and nasal tissue derived from RM. After differentiation for two-weeks at an air-liquid interface, tracheal epithelial cell (TEC) and nasal epithelial cell (NEC) cultures showed multiple types of cells, beating cilia, mucus production and intact tight junctions. Infection of TEC cultures with MV showed massive shedding of multi-nucleated giant cells into the apical compartment. Infectious virus was detected in the shed cells and in fluid from the apical, but not the basolateral compartment. The growth kinetics of MV in TEC cultures showed an increase in viral production 2-3 days after infection and then sustained virus production until the end of the study (8 days pi). Similar growth kinetics and peak titers (~10^5 TCID50/ml) of infectious virus were recovered from the apical supernatant following MV infection of paired TEC and NEC cultures derived from the same monkey. In this study, we successfully established a protocol to grow TEC and NEC derived from RM in culture, which serves as a useful tool to complement in vivo macaque studies for respiratory vaccine delivery. Our study demonstrated that MV is able to replicate in both nasal and tracheal epithelial cells following infection through either the apical or basolateral surface.
*12. Kaitlin Rainwater Lovett

Kaitlin Rainwater-Lovett, Carolyn Bolton-Moore, Mwangelwa Mubiana-Mbewe, Hope Nkamba and William J. Moss

**Changes in measles serostatus among HIV-infected Zambian children initiating antiretroviral therapy before and after the 2010 measles outbreak**

Influenza vaccines are critical for reducing morbidity and mortality associated with annual influenza epidemics. These vaccines protect primarily by inducing neutralizing antibodies targeting the hemagglutinin (HA) protein. Current influenza vaccines provide good protection from infection with antigenically matched virus strains but provide limited protection when circulating virus strains undergo either antigenic shift or drift. The extracellular domain of the M2 protein has been proposed as a potential universal vaccine target due to its conserved nature and the ability of antibodies that recognize this domain to protect animals from influenza A virus infection. To further investigate M2 ectodomain (M2e) based influenza A virus vaccines, various M2e sequences have been inserted into the hypervariable region 5 (HVR5) of the hexon capsid protein of recombinant adenovirus serotype 5 (Ad5) in order to create a replication competent vaccine that displays M2e sequences on the surface of the virion. Concurrently, the functional significance of the M2e domain is being determined by creating MDCK cell lines stably expressing M2 proteins containing various mutations in the extracellular domain. M2 proteins containing alanine substitutions at residues 2-4, 5-7, 18/20-21 and 22-24 in the M2 ectodomain were able to complement the replication of M2-null viruses, demonstrating that they are not critical for M2 function. Using these approaches, we will identify sequences important for M2e immunogenicity and function, thereby providing important insights into the role that M2 plays in the viral life cycle.

*13. Andrew Mirelman

Meghan L. Stack, Sachiko Ozawa, David M. Bishai, Andrew Mirelman, Yvonne Tam, Louis Niessen, Damian G. Walker, and Orin S. Levine

**Estimated Economic Benefits During The ‘Decade Of Vaccines’ Include Treatment Savings, Gains In Labor Productivity**

In 2010 the Bill & Melinda Gates Foundation announced a $10 billion commitment over the next ten years to increase access to childhood vaccines in the world’s poorest countries. The effort was labeled the “Decade of Vaccines.” This study estimates both the short- and long-term economic benefits from the introduction and increased use of six vaccines in seventy-two of the world’s poorest countries from 2011 to 2020. Increased rates of vaccination against pneumococcal and *Haemophilus influenzae type b* pneumonia and meningitis, rotavirus, pertussis, measles, and malaria over the next ten years would save 6.4 million lives and avert 426 million cases of illness, $6.2 billion in treatment costs, and $145 billion in productivity losses. Monetary estimates based on this type of analysis can be used to determine the return on investment in immunization from both the international community and local governments, and they should be considered in policy making.

*14. Andrew Mirelman

Sachiko Ozawa, Meghan L. Stack, David M. Bishai, Andrew Mirelman, Ingrid K. Friberg, Louis Niessen, Damian G. Walker, and Orin S. Levine

**During The ‘Decade Of Vaccines,’ The Lives Of 6.4 Million Children Valued At $231 Billion Could Be Saved**

Governments constantly face the challenge of determining how much they should spend to prevent premature deaths and suffering in their populations. In this article we explore the benefits of expanding the delivery of life-saving vaccines in seventy-two low- and middle-income countries, which we estimate would prevent the deaths of 6.4 million children between 2011 and 2020. We present the economic benefits of vaccines by using a “value of statistical life” approach, which is based on individuals’ perceptions regarding the trade-off between income and increased risk of mortality. Our analysis shows that the vaccine expansion described above corresponds to $231 billion (uncertainty range: $116–$614 billion) in the value of statistical lives saved. This analysis complements results from analyses based on other techniques and is the first of its kind for immunizations in the world’s poorest countries. It highlights the major economic benefits made possible by improving vaccine coverage.
*15. Andrea Radtke
Andrea J. Radtke, Sze-Wah Tse, Diego Espinosa, Yun-Chi Chen, Photini Sinnis, Fidel Zavala, Ian Cockburn

**Vaccination with attenuated malaria sporozoites: Migration to skin-draining lymph nodes is required for CD8+ T cell priming**

Vaccination with irradiated sporozoites elicits protective CD8+ T cell responses against malaria. The priming and differentiation of CD8+ T cells depends on the first interactions between naïve T cells and professional antigen presenting cells (APCs). Therefore, a major focus of vaccine research is the identification of the antigen presenting events critical for CD8+ T cell priming. Using a murine model of malaria infection, we have demonstrated that antigen specific CD8+ T cells are primed by dendritic cells in the lymph nodes draining the site of inoculation. To determine whether sporozoite migration to the draining lymph node and/or lymph node migration of antigen bearing skin-derived dendritic cells are required for CD8+ T cell priming, we created a transgenic *Plasmodium berghei* parasite that is unable to exit the dermis and therefore does not reach the draining lymph node or liver (*P. berghei* CS\textsuperscript{SMA\textsubscript{M}}\textsubscript{N}). Intradermal inoculation of *P. berghei* CS\textsuperscript{SMA\textsubscript{M}}\textsubscript{N} sporozoites failed to induce robust antigen specific CD8+ T cell responses in wild type mice as compared to control sporozoites. These studies strongly suggest that sporozoite migration to the draining lymph nodes is a critical factor for CD8+ T cell priming following sporozoite immunization.

*16. Rakshani, Noor

**Factors associated with timely initiation and completion of childhood immunization schedule among children in Pakistan: An Analysis of the Pakistan Demographic and Health Survey 2006-07 Data.**

Context: Pakistan is challenged to reduce its infant mortality and meet the Millennium Development Goals. Vaccines have proven their merit in reducing childhood deaths. According to the Pakistan Demographic and Health Survey 2006-07 by 12 months of age 80% of children receive BCG vaccine and 75% receive DPT1 vaccine but only 56.1% receive DPT3 and only 39.2% receive the complete schedule. Pakistan needs to reach the WHO minimum criteria of 90% coverage at the national level.

Objective: To identify the maternal, child and socio-economic correlates associated with immunization completion in Pakistan by analyzing a nationally representative sample using the PDHS 2006-07 data.

Design: The PDHS 2006-07 was a two stage stratified random sample survey that took place from September 2006-April 2007. Logistic regression analysis technique was applied to see the association of maternal, child and household correlates to receiving DPT3. Design based analysis was utilized to account for the complex survey design of the Pakistan DHS 2006.

Setting: Nationally representative sample of 9720 households in the urban and rural areas of Pakistan.

Study Participants: Ever married women ages 12-49 years, one woman from each 9720 households.

Outcome measure: Children who received the third dose of DPT vaccine

Results: A total of 1692 children 12-23 months of age were in the sample and of these 1104 received DPT1 and 872 had received DPT3. After adjusting the correlates most significantly associated with receiving DPT3 were: i) child having health card and was seen at the time of interview (OR 53.7 95%CI 27 – 105 p-value 0.00), ii) maternal education of primary or less and secondary or more (OR 2.5 95%CI 1.6 – 4 p-value 0.00) and iii) wealth index of middle class or less and rich or higher (OR 1.5 95% CI 1.0 – 2.2 p-value 0.00).

Conclusion: Having a health card is most significantly associated with receiving DPT3 after adjusting for other factors like maternal education and socio-economic status.

*17. Amritha Ramakrishnan

Amritha Ramakrishnan, Margaret Inokuma, Vernon C Maino, Andrew Pekosz and Jay H Bream

**Cellular immune response to seasonal influenza vaccines**

Influenza is a globally important respiratory pathogen that continues to cause a staggering 3 to 5 million infections worldwide. The currently licensed seasonal vaccines are efficacious in preventing infection against antigenically related strains of virus, however, the mechanisms contributing to protective immunity, particularly cross-protective immunity are not well understood. While antibody responses have been the focal point of vaccine studies in humans, numerous studies in animals suggest that T cell are also important in mediating viral clearance and recovery from infection. Importantly, T cells are thought to be the key mediators of heterotypic or...
cross-protective immunity. Yet, there is only limited data on cellular immunity to influenza in humans and the impact of vaccination on such responses is not well understood. Accordingly, we sought to characterize the cellular immune response to seasonal influenza vaccines in healthy adults. We were specifically interested in understanding how different vaccine formulations (TIV vs LAIV) affect the development of functionally (as measured by their ability to secrete multiple effector cytokines) and phenotypically different T cells. In the present study, we describe a novel, high-throughput assay system to characterize antigen specific T cells from PBMCs using whole virus and peptide-based stimulations. Using this assay, we have begun functional and phenotypic characterization of influenza specific T cells in participants who received either TIV or LAIV during the 2006-7 and 2007-8 influenza seasons. We hope that this study will provide insight into how different vaccine strategies impact the development of cellular immunity. This could prove valuable in designing new vaccines for influenza as well as other infectious diseases.

*18. Sze-Wah Tse

Sze-Wah Tse, Ian Cockburn, Yun-Chi Chen, Andrea Radtke and Fidel Zavala

Role for CXCR6 on the residency of memory CD8+ T cells after irradiated Plasmodium sporozoite vaccination

Liver resident memory CD8+ T cells are important for immunity against pre-erythrocytic stage malaria parasites as they could quickly respond and eliminate parasitized hepatocytes. Therefore, the establishment of this resident memory population is crucial to anti-malaria protective immunity. Using a murine malaria model and a microarray approach, we identified up-regulation of several genes, including the chemokine receptor Cxcr6, on memory CD8+ T in the liver after vaccination with irradiated Plasmodium sporozoites. Interestingly, we also found a reduced number of malaria specific CD8+ T cells in the liver of Cxcr6-/- animals. Furthermore, we concluded that CXCR6 played an intrinsic role on CD8+ T cells in mice after irradiated sporozoite immunization. While CD8+ T cells deficient of CXCR6 did not display any defects in cytokine production, mice with Cxcr6-/- memory CD8+ T cells were more susceptible to live parasite challenge. In conclusion, these data suggest CXCR6 plays an important role in CD8+ T cell homing and residency in the liver and therefore may have a significant role in maintaining the anti-malaria CD8+ T cell population in this organ.

19. Billy Fischer

Fischer II, W., King, L.S., Lane, A., Pekosz, A.

Characterization of Attenuated Virus Production during LAIV Infection of Primary, Differentiated Human Nasal Epithelial Cells

Live Attenuated Influenza Vaccine (LAIV) strains are vaccines intranasally administered that elicit a robust mucosal innate immune response without causing clinical disease. While many of the mutations associated with the cold adapted, temperature sensitive and attenuated phenotypes have been studied in non-human or immortalized cell cultures, the actual mechanism of attenuation is poorly understood. Using a novel primary, differentiated human nasal epithelial cell (hNEC) culture system we compared the replication kinetics, levels of cell-associated and secreted viral proteins, and the amount of viral RNA incorporated into secreted viral particles during infection with LAIV and the corresponding wild type (WT) influenza viruses. Growth curves generated at 33°C and 37°C revealed significantly more infectious virus production in hNEC and MDCK cultures infected with seasonal H1N1 virus than with LAIV. The difference in infectious virus production was much greater in hNEC cultures than MDCK cells, indicating LAIV attenuation may be more pronounced in the primary cell culture system. Despite the disparity in infectious virus production, an equivalent level of cell-associated and secreted viral proteins HA, M2, and M1 were found with both viruses, suggesting the formation of non-infectious virus particles by LAIV. There was a greater level of M segment RNA incorporated into secreted virus particles during infection with WT virus compared with LAIV infection. Taken together our results suggest that the mechanism underlying the LAIV’s ability to elicit an immune response without causing an overt clinical phenotype is due to the production of non-infectious viral particles resulting from impaired viral RNA packaging.
**The Johns Hopkins Vaccine Initiative**

**Vaccine Day 2011 Poster Session**

20. Brandon Brown  
Brandon Brown, Magaly Blas, Cesar Carcamo, Neal Halsey

**HPV prevalence, HPV4 completion, and immune response among Peruvian female sex workers**

**Background:**
- Persistent HPV infection is found in nearly all cervical cancer cases (1)
- HPV vaccines have been shown to be highly efficacious against CIN associated with types 16 and 18 in women not infected at the time of immunization (2)
- FSWs at high risk of HPV infection due to exposure to multiple sexual partners, with worldwide DNA prevalences ranging from 2-100% (3-9)
- FSWs in Peru encouraged to receive RPR testing every 3 months and HIV testing every 6 months
- We provided HPV vaccine in two schedules to FSWs in Lima, Peru; collected serum before and after vaccination to estimate the change in antibody levels; and compared those levels with HPV DNA status

**Subjects:** FSWs recruited in 2009-10 from 49 locales in Lima, Peru. Inclusion criteria-FSW age 18-26 years, no immune disorder, and not pregnant. Participants randomized to HPV4 in a standard (0,2,6 month) or modified schedule (0,3,6 m).

**Data collection:** Convenience sampling with standardized questionnaires. Cervical swabs collected at Day 0, 5ml blood collected at Day 0 and month 7.

**Analyses:** Cervical samples sent to JHSPH for Linear Array testing, serum sent to PPD for cLIA testing. Chi2 tests for variables by baseline serostatus. HPV DNA and serology association calculated using Fisher’s exact tests. Comparison of antibody titers using t-tests on log transformed data. Association of variables with antibody response calculated using linear regression on log transformed titers.

**Conclusions:**
- Female sex workers (FSWs) in Lima, Peru had a high seroprevalence of HPV 6/11/16/18 (vaccine genotypes), likely due to exposure to HPV with several clients, brothel owners, and high risk partners with varying levels of condom use.
- High baseline HPV seroprevalence compared to DNA prevalence confirms DNA is a poor predictor of HPV exposure.
- We achieved high HPV vaccine completion rates in a sample of FSWs in Lima, Peru. Significant recruitment and retention efforts may be necessary to achieve similar results in FSWs or other high risk groups in other countries, and at a larger scale.
- A modified vaccination schedule provided equivalent immune responses, and is convenient if paired with 3 month RPR visits.
- High vaccine genotype seroprevalence at baseline highlights that women should be vaccinated before sexual debut for maximum protection.

21. Dagna Constenla  
Mark Connolly, Dagna Constenla

**Assessing economic benefits for government and society attributed to malaria investment strategies: An exploratory analysis based on malaria vaccination**
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22. Andrea DeLuca


The Pneumonia Etiology Research for Child Health (PERCH) Project

Pneumonia is the leading cause of death from infectious disease for children world-wide. Existing knowledge on the etiologies of
coldhood pneumonia is largely based on studies from the 1980s and 1990s. With expanded use of new pneumonia vaccines and
changes in host and environmental factors, a new evidence base that harnesses novel technologies for diagnosis is needed.
PERCH is a multi-center case-control study of the etiology of severe & very severe pneumonia in children aged 1-59 months. Over
two years, PERCH will enroll approximately 6,500 hospitalized cases with WHO-defined severe and very severe pneumonia.
Approximately the same number of community-based controls will be enrolled to assess the community prevalence of pathogens as
well as known and unstudied risk factors for pneumonia.

This study will be carried out using standardized clinical and laboratory methods and techniques, in combination with innovative
diagnostic and specimen collection methods. The data will be analyzed using advanced statistical methods and their interpretation
will be considered in advance of knowing the specific microbiologic results. Conducting PERCH now, strategically designed to reflect
what we expect the world to look like in 2015 and beyond, will provide important evidence to guide the next generation of
pneumonia prevention and treatment approaches.

23. Anna Durbin

Anna Durbin, Beth Kirkpatrick, Daniel Elwood, Kristen Pierce, Kimberli Wanionek, Bhavin Thumar, Marya Carmolli, Catherine Luke,
Kanta Subbarao, Steve Whitehead

A tetravalent live attenuated dengue vaccine based on the 3'-UTR Δ30 mutation is safe and immunogenic against all 4 serotypes
in humans

Dengue virus (DENV) has become the most important arbovirus worldwide with a 30-fold increase in DENV infections and hundreds-
fold increase in severe disease. The goal of the National Institutes of Allergy and Infectious Diseases intramural DENV vaccine
program is to produce a minimally reactogenic, immunogenic, genetically stable, tetravalent live attenuated DENV vaccine that is
cost-effective and safe for the community. Over the past eleven years, the laboratory has developed numerous live attenuated
candidate vaccines against the four individual DENV serotypes using a variety of techniques based on the delta-30 mutation in the 3’
untranslated region of the genome. We have tested 8 monovalent vaccines in 14 separate Phase I clinical trials to identify vaccine
candidates that are safe and maintain optimal infectivity and immunogenicity profiles for inclusion in a tetravalent formulation.
Each monovalent candidate was well tolerated by volunteers with no volunteer experiencing a dengue-like illness or vaccine-related
serious adverse events. Infectivity, immunogenicity, and reactogenicity were used to determine which vaccine candidates were
appropriate for inclusion in a tetravalent formulation. A Phase I clinical trial evaluating four different tetravalent admixtures given as
a single dose of 1000 PFU/serotype was conducted in adult subjects. Preliminary data indicates that the admixtures remained
minimally reactogenic and seroconversion rates of 50 - 100% were observed for each of the four DENV serotypes. After a single
doze, the lead admixture induced a tetravalent immune response in 40% of volunteers and at least a trivalent immune response in
90% of volunteers. Administration of a second vaccine dose at a six month interval is currently underway to determine the
feasibility of increasing the seroconversion rates and extending the durability of the immune response.

* denotes student posters eligible for the poster competition
24. Lindsay Grant
Grant LR, O’Brien SE, Weatherholtz RC, Campbell JJ, Reid R, Santosham M, O’Brien KL

Early Impact of PCV13 on Nasopharyngeal Colonization among American Indian Children and Household Members of the Navajo and White Mountain Apache Communities

Background
7-valent pneumococcal conjugate vaccine protects against nasopharyngeal (NP) colonization with vaccine serotypes. The 13-valent pneumococcal conjugate vaccine (PCV13) was licensed on February 24, 2010 and introduced in March among Navajo and White Mountain Apache (N/WMA) communities. This study evaluates the impact of PCV13 against serotype-specific NP colonization in the 2 years following vaccine introduction.

Methods
N/WMA children (7<24m) and their family members enrolled into this prospective, community-based, cross-sectional NP study. Using continuous enrollment before and throughout PCV13 introduction, an NP swab was collected from each study participant. Pneumococci are isolated by culture following broth enrichment and serotyped by Quellung reaction. Statistical analyses compare the prevalence of overall, vaccine-type and non-vaccine-type NP colonization before and after PCV13 introduction.

Results
Enrollment began in January 2010 and will continue through March 2012 when an estimated 6200 participants will have been recruited. As of August 16, 2011, 4818 participants have been enrolled (N=1435, <2 years; N=1001, 2-7 years; N=376, 9-17 years; N=1871, 18-49 years; N=135, 50+ years). Analyses of NP specimens collected from January 2010 through February 2011 demonstrate that 35% (1028/2902) of study participants are colonized with pneumococcus (55%, <2 years; 55%, 2-7 years; 32%, 8-17 years; 13%, 18-49 years; 16%, 50+ years). Of the pneumococci isolated (N=1029), 18% (N=183) are PCV13 vaccine-type of which 46% (N=85) were isolated among children <2 years of age. Serotype 19A is the most frequently isolated serotype overall (N=100) and from children <2 years (13%, N=60/477).

Conclusions
NP colonization remains very common among N/WMA children through 8 years of age. Serotype 19A is the most frequent colonizing serotype among N/WMA of all ages, but particularly among young children. Serotype-specific NP colonization data from the first 12 months of PCV13 use will be presented to establish if an early impact is observed.

25. Lindsay Grant

Efficacy of pentavalent human-bovine reassortant rotavirus vaccine among American Indian children

Background
Acute gastroenteritis (AGE) is a significant global health problem among children with rotavirus contributing to a majority of the AGE burden. Historically, Native American infants have had higher rates of rotavirus AGE compared to general United States population.

Methods
From 2002-2004, Navajo and White Mountain Apache (N/WMA) American Indian infants 6-<12 weeks of age were enrolled into the phase-III, double-blind, placebo-controlled efficacy trial of pentavalent human-bovine reassortant rotavirus vaccine (PRV). Participants received three doses of vaccine or placebo with 28-70 days separating each dose. Active surveillance identified AGE episodes after enrollment and serious adverse events (SAEs) within 42 days after each dose. AGE was defined as 3 or more watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting. Stool specimens from AGE episodes were tested for rotavirus by an enzyme immunoassay and serotyped. AGE severity was determined by a 24-point clinical scoring system.

Results
We enrolled 1,008 N/WMA infants; 509 received PRV, 494 placebo and 5 were not dosed. Among placebo recipients, the rotavirus AGE incidence was 118.3/100,000 child-years; the percent of AGE caused by serotypes G1, G2 and G3 was 76%, 22% and 2%, respectively. The efficacy of PRV against rotavirus AGE caused by serotypes G1-G4 was 77.1% (95% confidence interval [CI]: 59.8-
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87.6. PRV prevented 89% (95% CI: 65.9-97.9) of moderate-to-severe (severity score 9-16) and severe rotavirus AGE (severity score >16). There were no cases of intussusception or death within the 42 day safety reporting period.

Conclusions
PRV is highly efficacious against rotavirus AGE caused by vaccine serotypes and moderate and severe AGE among N/WMA children, a group at high risk of rotavirus AGE. PRV demonstrated an excellent safety profile.

26. Laura Hammitt

Pneumonia etiology among hospitalized children in Kilifi, Kenya

Background: Pneumonia is the leading cause of childhood death in the developing world. Better etiology data are required to reduce this mortality burden.

Methods: We conducted a case-control study of pneumonia etiology among children aged 1–59 months in rural Kenya. Cases were hospitalized with WHO-defined severe pneumonia (SP) or very severe pneumonia (VSP); controls were outpatient children without pneumonia. We collected blood for culture, induced sputum for culture and multiplex PCR, and oropharyngeal swabs for multiplex PCR from cases, and serum for serology and nasopharyngeal swabs for multiplex PCR from cases and controls.

Results: 810/984 (84%) eligible cases were enrolled in the study; 232 (29%) had VSP. Blood cultures were positive in 52/749 (7%) cases. A predominant potential pathogen was identified in sputum culture in 70/417 (17%) cases. A respiratory virus was detected by PCR of nasopharyngeal swabs in 486/805 (60%) cases and 172/369 (47%) controls. Only RSV showed a statistically significant association between virus detection in the nasopharynx and pneumonia hospitalization (odds ratio 12.5, 95%CI: 3.1, 51.5). Among 257 cases in whom all specimens (excluding serology) were collected, bacteria were identified in 24 (9%), viruses in 137 (53%), mixed viral/bacterial infection in 39 (15%), and no pathogen in 57 (22%); bacterial causes outnumbered viral causes when results of the case-control analysis were considered.

Conclusions: A potential etiology was detected in >75% of children admitted with SP or VSP. Except for RSV, the case-control analysis did not detect an association between viral infection of the nasopharynx and hospitalized pneumonia.

27. Clayton Harro

Clayton Harro, David Sack, Michael Darsley, August Bourgeois, Barbara DeNearing, Andrea Feller, Subhra Chakraborty, Alicia Marcum, Ruval Comendador, Charlotte Buchwaldt, and Richard Walker

Volunteers receiving live attenuated ETEC vaccine (ACE527) have reduced severity of illness following H10407 challenge

Background: Enterotoxigenic E. coli (ETEC) is a major contributor to morbidity, mortality, and malnutrition associated with infectious diarrhea in less-developed countries. ETEC is also responsible for approximately 50 percent of diarrhea in travelers to these countries. Data from studies of natural infection and from experimental challenge studies indicate that immunoprophylaxis via vaccination is feasible. In a previous dose-escalation trial, an orally administered, trivalent, live attenuated ETEC vaccine (ACE527) met pre-defined safety and immunogenicity criteria for advancement to a Phase IIb immunization and challenge study.

Methods: A double-blind, placebo-controlled trial was conducted in adult volunteers at the Johns Hopkins University Center for Immunization Research. The primary objective was to determine whether ACE527 vaccination produced a statistically significant reduction in moderate to severe ETEC illness induced by ETEC H10407, a wild type, ST/LT toxin-positive ETEC strain expressing CFA/I antigen. A total of 70 subjects were randomized to receive 3x10^{10} cfu of each strain (10^{11} cfu total dose) of ACE527 (N=36) or placebo (N=34) at Study Days 0 and 21. Of these, 56 subjects were challenged on Study Day 49 (28 days after the second dose) with ETEC H10407 (~2x10^7 cfu) administered orally in bicarbonate. Monitoring procedures assessed vaccine-associated safety, shedding, and immunology, as well as post-challenge clinical outcomes, stool microbiology (ETEC H10407 excretion), and ETEC-specific immunology. All volunteers were supported clinically as necessary and received antibiotic treatment (ciprofloxacin 500 mg twice daily for three days) beginning five days after ETEC H10407 challenge or sooner based on protocol-directed criteria.

Results: ACE527 induced strong immune responses to LT-B and the CFAs expressed on all three vaccine strains. Immune responses to LT-B and CFA/I were at least as good as those induced by challenge of naive subjects with ETEC H10407. The observed protective
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Efficacy of the vaccine against ETEC H10407-associated moderate-to-severe diarrhea was 26.5% (95% CI of -13 to 52%; P = 0.12), with the rate in placebos being 70.4% and in vaccinees 51.7%. However, a clear biological effect of vaccination was observed. Vaccine recipients were 73% more likely to be diarrhea-free than placebo recipients after challenge (45% versus 26% of subjects respectively; P = 0.04). There was also a reduction in the total amount of diarrheal output among vaccinees (P = 0.06), an effect seen during the first 24 hours after the onset of symptoms as well as during the total 120-hour observation period. There was a significant reduction in the level of colonization among vaccinees by the challenge bacteria (P = 0.001) as measured by bacterial shedding in the stool on day two post-challenge.

No study-related serious adverse events occurred, and there were no early terminations/withdrawals due to vaccine safety or tolerability. Vaccine-associated adverse events were similar to those seen previously. Gastrointestinal adverse events (nausea, vomiting, diarrhea) occurred with greater frequency in vaccinees than in placebo recipients, although only the increased incidence in vomiting was statistically significant, occurring predominantly on the day of vaccination and resolving spontaneously within 24 hours. Vaccine colonization was self-limiting with median time to negative stool culture post-immunization < 1 week after each dose.

**Conclusions:** ACE527 induces clinically significant attenuation of ETEC illness and reduces ETEC intestinal colonization in a stringent ETEC H10407 human challenge model. The vaccine is safe when administered orally at a total dose of 10^{11} cfu, though further refinement of dosage and formulation is warranted in conjunction with expanded trials in at-risk traveler and endemic populations.

28. Sarah O’Brien

**Longterm Impact of Pneumococcal Conjugate Vaccine on a Population at High Risk for Pneumococcal Disease**

**Purpose:** Before pneumococcal conjugate vaccine (PCV), Navajo had invasive pneumococcal disease (IPD) rates 3- to 5-fold those of the general US population; only 50% of IPD cases among children <2 years were caused by serotypes in the PCV7 vaccine (i.e. vaccine serotypes (VT), 4, 6B, 9V, 14, 18C, 19F, 23F). We aimed to assess the impact of routine PCV7 use.

**Methods:** Active, laboratory, population-based surveillance for IPD was conducted at hospital facilities serving the Navajo Nation; a case was defined as pneumococcus cultured from a normally sterile site in an American Indian person. Isolates were serotyped by Quellung or PCR and charts abstracted for clinical and demographic information. Indian Health Service (IHS) User Population denominators were used for rate calculations. IPD cases from 1995-97 (pre-PCV era) and 2007-09 (routine use PCV era) were compared.

**Results/Outcomes:** We identified 469 IPD cases in 1995-97 and 369 in 2007-09, a 21% reduction in average annual cases. The annual rate of VT-IPD in children <5 years fell from 124 to 1 case/100,000 (P<0.0001). The non-VT IPD rate remained unchanged in all age-groups except those 40-<65 years who experienced a 23% increase (P=0.03). Among those <2 years, serotypes 7F (9 vs. 52 cases/100,000 per year, P=0.002) and 19A (9 vs. 37 cases/100,000 per year, P=0.02) increased while serotype 5 decreased (55 vs. 0 cases/100,000 per year, P<0.001).

**Conclusions:** VT IPD has been eliminated in the PCV7 era. Minimal serotype replacement has occurred. We are evaluating the impact of PCV13 on the remaining disproportionate morbidity of IPD.

29. Daniel Park
Kagucia E, Park DE, for the Post-Conjugate Vaccine Pneumococcal Serotype Project team

**Review of changes in incidence of serotype-specific pneumococcal disease following routine pneumococcal conjugate vaccine introduction**

In many places where the pneumococcal conjugate vaccine (PCV) has been introduced, invasive pneumococcal disease (IPD) caused by pneumococci of serotypes included in PCV (VT) has virtually disappeared. In contrast, many sites have seen an increase in the incidence of invasive disease caused by nonvaccine-serotypes (NVT). These increases in NVT pneumococcal disease have been interpreted as representing “serotype replacement”. Other factors, such as outbreaks and changes in surveillance systems, can also cause changes in NVT. Through a systematic analysis of datasets of IPD from before and after PCV introduction, the magnitude and consistency of changes in serotype-specific IPD can be clarified. We identified relevant datasets from literature review and word-of-
mouth among pneumococcal experts. Data was collected from eligible sites in a structured format. We calculated rate ratios (RR) for each site by dividing post-PCV IPD rates for 3 periods (1-2, 3-4, 5+ years after PCV introduction) by pre-PCV rates. Results from 29 datasets from 5 WHO regions showed that among children < 5 years old a VT IPD RR<1 in over 95% of sites and <0.5 for over 90% of sites by 3 years post-introduction. VT IPD declined with each subsequent time period after introduction with a median RR of 0.10 at 3-4 years post and 0.06 at 5+ years post. Conversely, NVT IPD increased with time with a median RR of 1.7 at 3-4 years post and 2.3 at 5+ years post. Overall IPD (VT + NVT IPD) was decreased (RR<1) in 80% of sites at 3+ years after vaccine introduction – median RR of 0.64 at 3-4 years post and 0.85 at 5+ years post. We will refine our analysis in children by limiting to sites with at least 2 years of pre-introduction data and 3 years post-introduction data and among sites with >70% vaccine coverage. We will further evaluate serotype-specific IPD changes in finer age strata, including among adults, and the effect of vaccine dosing schedules and explore surveillance artifacts that may impact the results.

30. Daniel Park

Park DE, Knoll MD, Johnson S, Chandir S, Goldblatt D, Loo J, Whitney CG, O’Brien KL and the Pneumococcal Conjugate Vaccine Dosing Landscape Analysis Project team

Landscape analysis project: Evaluating the effects of different pneumococcal conjugate vaccine dosing schedules on immunogenicity

*Streptococcus pneumoniae* is a leading cause of childhood mortality worldwide. Despite the breadth of studies demonstrating the benefits of pneumococcal conjugate vaccine (PCV) introduction, there is a lack of consensus on the optimal PCV dosing schedule in children in various epidemiologic settings. We conducted a comprehensive review and analysis of the available literature on PCV dosing regimens and their effect on immunogenicity. Data was double-abstracted from studies published after 1994 and known unpublished studies. 136 citations met the following inclusion criteria: at least 2 doses of PCV with the first dose at 4 months of age or younger and the second dose at 6 months of age or younger, non-high risk study population, and a vaccine product that is 7-valent or higher (except for Aventis PCV10). Effect of number and timing of doses on geometric mean antibody concentration (GMC) against vaccine serotypes 1, 5, 6B, 14, 19F and 23F was assessed using random effects linear regression adjusted for PCV product, co-administration with DTaP versus DTwP, lab method and geographic region. Thirteen studies used a 2-dose primary schedule with no booster in the 2nd year of life (“2+0”), 16 used a 2+1 (i.e., with booster) schedule, 47 used a 3+0 schedule, and 60 used a 3+1 schedule. The 3-dose primary schedule consistently produced higher post-primary GMC antibody response than the 2-dose schedule for all serotypes except for serotype 1. Comparing 3-dose schedules, the post-booster antibody response of a 2+1 schedule was significantly higher than the post-primary response of a 3+0 schedule for all serotypes. While giving the 3rd dose in the 2nd year of life produces a higher antibody response than if it is given in the 1st 6 months, the lower GMC during the period between the last primary dose and booster dose may increase risk of pneumococcal disease. This risk may warrant introduction using a 3+0 schedule initially followed after several years by a shift to the 2+1 schedule.

31. Debbie Persaud

**Stability of Resting CD4+ T Cell HIV-1 Reservoirs following Immunization With Recombinant Poxvirus HIV-1 Vaccines**

32. Kawsar Talaat

Surender Khurana, Nitin Verma, Kawsar R. Talaat, Ruth A. Karron, and Hana Golding

**Immune response following H1N1pdm09 vaccination: differences in antibody repertoire and avidity in young and elderly populations stratified by age and gender**

**Background:** The H1N1 2009 influenza (H1N1pdm09) pandemic had several unexpected features including lower morbidity and mortality in older populations.

**Methods:** We performed in-depth elucidation of antibody responses generated following H1N1pdm09 vaccination in elderly (66-83 years) and younger (18-45 and 46-65 years) adults using H1N1pdm09-whole genome-fragment phage display library (GFPDL), and measured antibody isotype and affinity to antigenic domains within hemagglutinin (HA).

**Results:** H1N1pdm09 vaccination induced 10-fold higher antibody levels in elderly compared to younger adults. These antibodies primarily targeted the HA1 globular domain, including neutralizing epitopes in the receptor binding domain. Antibody epitope repertoire, isotype and affinity maturation following H1N1pdm09 vaccination evolved independently for HA2, HA1, and HA1 N-

* denotes student posters eligible for the poster competition
terminus antigenic regions. Post-vaccination sera from elderly demonstrated substantially higher avidity than from younger subjects (>60% vs. <30% 7M urea resistance, respectively) and slower antibody dissociation rates using Surface Plasmon Resonance. We also identified a gender difference in post-vaccination antibody avidity (females < males) in adults < 65 yrs.

**Conclusions:** This is the first study in humans that provides evidence for a qualitatively superior antibody response in the elderly following H1N1pdm09 vaccination. These findings may help explain the age-related mortality observed during the H1N1pdm09 pandemic. The difference in gender-specific avidity merits further exploration.

33. Chizoba Wonodi
Chizoba Wonodi, Muyi Aina, Gbolahan Oni, Tope Olukowi, Cecily Stokes-Prindle, Orin Levine , Lois Privor-Dumm

**Landscape Analysis of Routine Immunization in Nigeria. Breaking bottlenecks and barriers**

Abstract: Nigeria has high under-five mortality, with 185 child deaths per 1,000 live births. A significant portion of those deaths are preventable through routine immunization (RI); coverage of routine childhood vaccines in many parts of Nigeria is among the lowest in the world. Although there have been recent improvements in immunization coverage rates, at the end of 2010 nearly 1.5 million children remained unvaccinated.

This qualitative analysis compiles data from 117 key informant interviews and 11 focus groups in 8 Nigerian states in order to identify key supply-side constraints and demand-side determinants of RI coverage rates and examine potential solutions.

34. Chizoba Wonodi
Wonodi C.B., Privor-Dumm L, Aina M, Pate A.M., Reis R, Gadhoke P and Levine O.S

**Using Social Network Analysis To Examine The Decision-Making Process On New Vaccine Introduction In Nigeria.**

The decision making process to introduce new vaccines into national immunization programs is often complex, involving a range of stakeholders who act to provide technical information, mobilize finance, implement vaccine programs and garner political support. Stakeholders may approach the decision making process with different levels of interest, knowledge and motivation. Lack of consensus on the priority, public health value or programmatic feasibility of adding a new vaccine can delay policy decisions.

Efforts to support country-level decision-makers make the case for new vaccine introduction have largely focused on providing data inputs, like disease burden and economic benefits data. Less attention has been given to understanding the policy process as it relates to interactions of policy actors and how the distribution of influence can be harnessed to support rational and efficient decision-making.

Social network analysis is a social science technique concerned with explaining social phenomenon using the structural and relational features of the network of actors involved. We interviewed government officials at the federal and State level in Nigeria as well as officers of bilateral and multilateral partners and other stakeholders like the media and health providers, to describe formal and informal relationships and the distribution of influence among vaccine decision makers. We used social network analysis to explore linkages and pathways to stakeholders who can influence critical decisions in the policy process such as assuring sustainable financing and strengthen program implementation.

Our findings suggest a relatively robust engagement of key stakeholders in Nigeria, but with ample opportunities to strengthen decision-making and generate broader support for vaccine introduction by increasing the involvement of some key stakeholders. Specifically, our results suggest financial stakeholders like the Ministry of Finance could be brought in to a central role and that implementation stakeholders should be more involved at the federal-level policy formulation.