Vaccination News from ICAAC 2006

(Abstract #)

Innate immunity:

(1265) The immune system is ignorant or even unresponsive to most foreign proteins that are injected in a soluble, deaggregated form, but when injected together with an adjuvant, these foreign proteins can generate robust immunity and long-lived memory to the antigen. In fact, the nature of the adjuvant is what determines the particular type of immune response that follows, which may be biased towards cytotoxic T-cell responses, antibody responses, particular classes of T-helper responses, or antibody isotypes. Clearly, the ability of a vaccine to skew the response toward a particular type is of paramount importance, because different pathogens require distinct types of protective immunity. Central to this issue is a rare but widely distributed network of cells known as dendritic cells. These cells, which have been called "Nature's adjuvants", express pathogen recognition receptors, such as the Toll-like receptors and C-type lectins, which enable them to sense and respond to microbes or vaccines. Dendritic cells have a fundamental role in initiating and controlling the quality and strength of the immune response. Emerging evidence suggests an important role for the distinct Toll-like receptors and C-type lectins in differentially regulating the Th1/Th2/T regulatory balance, by inducing distinct intracellular signaling networks within dendritic cells.

Whereas in the past, the development of vaccines went along with the Pasteur principles (isolate – inactivate – inject), the future will bring new ways of vaccine development, e.g. the "reverse vaccinology", which starts with the analysis of the pathogen's genome in order to look for possible vaccine candidate antigens. A good example is the research on a new Meningococcus group B vaccine, where genomics allowed the identification of 5 surface antigens as potential vaccine candidates. The increased knowledge of immunology allows the definition of optimal adjuvants for different antigens.

(1267) In addition to enhanced immunogenicity in young infants, the conjugate vaccines, unlike pure polysaccharide vaccines, were shown to prime infants for subsequent memory responses to a challenge with pure polysaccharide (thus mimicking "natural" challenge). It is this memory or "boostability" that is thought to mediate the long term protection afforded by conjugate vaccines.

The analysis of recent British efficacy data has finally lead to new English conjugate vaccination recommendations: with 2 months pentavalent basic vaccination + PNV7, with 3 months penta + Men C, with 4 months penta + PNV7, with 5 months MenC, with 12 months PNV7 + MenC.

BCG vaccination:

(G-156b) BCG vaccination has variable efficacy in preventing tuberculosis. Vaccination with 3 different BCG vaccines in Mexico resulted in the activation of different immune pathways that may affect long-term vaccine efficacy. Some of the known variation in BCG efficacy might therefore be due to differences among BCG strains.

Hepatitis A vaccination:

(G-131) Berna's virosomal hepatitis A vaccine showed excellent immunogenicity in children 12-15 months old. There was no interaction with co-administrated routine vaccinations.

Human Papillomavirus vaccine:

(1275) Although the genital tract is a component of the mucosal immune system, it displays several distinctive features not shared by other typical mucosal tissues and external secretions. Both male and female genital tract tissues lack inductive mucosal sites analogous to Peyer's plaques. Consequently, local humoral and cellular immune responses stimulated by infections are weak and with the exception of some antigens, repeated local intravaginal immunizations result in minimal humoral responses. In

contrast to typical external secretions such as intestinal fluid that contain secretory immunoglobulin A as the dominant isotype, semen and cervicovaginal fluid contain more IgG than IgA. Because a significant proportion of IgG in genital tract secretions is derived from the circulation, systemic immunization with microbial protein, glycoprotein, or polysaccharide antigens may provide protective IgG antibody-mediated immunity in the genital tract.

(1279) Several trials have shown the efficacy of vaccination with virus-like particles to prevent HPV infection and disease. Once an individual has been infected, neutralizing antibodies are unable to clear the infection (but may eventually prevent disease progression???). Numerous strategies to induce T-cell responses against the oncogenic viral E6 and E7 proteins are being tried, with the goal of developing therapeutic vaccines to prevent progression or clear residual disease.

(G-613) Administration of inactivated quadrivalent HPV vaccine was generally well tolerated in almost 12,000 9 to 26 year old vaccinees in Mexico. Compared with placebo, a modest increase in injection-site reactions and a modest increase in the incidence of transient low grade fever were observed.

(G-156d) HPV vaccine efficacy and safety was comparable among investigated individuals naïve to the corresponding types with baseline covariates (age, smoking status, lifetime number of sexual partners, day 1 STD or cervico-vaginal infection status, lactation status, pregnancy history, baseline HPV seropositivity, and abnormal Pap test diagnosis). This supports vaccination of young women with quadrivalent HPV vaccine across a broad range of baseline characteristics. Subjects previously exposed to vaccine HPV types experienced an increased immune response against the vaccine types.

Influenza vaccines:

(G-154) A dose escalation study in 27 lymphoma patients showed a potential benefit of a dose escalation from 15µg HA (standard vaccine) to 135µg HA for he neutralizing antibody response (neutralizing AB increase and mean AB titer) against influenza A virus. No serious adverse reactions were observed.

(G-156a) Influenza vaccination of pregnant women in the third trimester – as recommended in the USA - has showed a substantial impact on proven influenza, and all febrile respiratory illness, but not diarrheal illness, in both infants and mothers.

Meningococcal vaccination:

(G-130) GSK's 4-valent, tetanus-toxoid conjugated MenACWY vaccine showed good immunogenicity in adolescents 15-19 years of age.

(G-133) A three-dose schedule of MenC co-administrated with hexavalent vaccine at the age of 3, 5, and 11 months was immunogenic and safe both in term and preterm Italian infants. Almost 100% of the vaccinated subjects reached serum bactericidal titers of ≥128. Yet, no long term immunogenicity data is available.

(G-143) Over the last 15 years, New Zealand has experienced an epidemic with a single Meningococcus B clone (B:4:P1.7B,4). MeNZB®, an outer membrane vesicle vaccine directed against the epidemic strain, was safe and partially immunogenic in 6-10 weeks old infants. Sero-response was achieved in 53% and 69% after 3 and 4 doses, respectively. The vaccine can be co-administered together with routine immunizations.

Pertussis vaccination:

(G-134) In a day care pertussis outbreak, vaccinated children aged 3-5.5 years showed a protection rate of 92.5% (small numbers in the unvaccinated control group).

(G-139) A comparative European analysis of pertussis protection showed a vaccine efficacy of ≥80%. After the age of 10 years, a decline of protection was observed, probably due to missed booster vaccination at school entry. A booster dose at around age 10 years may therefore be considered.

(G-144) Because of recently observed increasing US rates of pertussis in infants too young to have received 3 doses of DTPa, safety and immunogenicity of a forth dose of DTPa administered shortly after birth was evaluated. This additional dose did not increase local or systemic reactions. However, it resulted in a significantly lower response rate to 3 out of 4 pertussis antigens at 7 and 18 months of age, and thus did not confer a serologic advantage. But…

(G-618a) In contrast to the above results, the additional administration of a monovalent Pa vaccine dose at birth in Germany significantly accelerated the serological response against pertussis (measured at age 3 months) in these infants without negatively affecting the response at later ages (i.e. no induction of immunotolerance to pertussis antigens). Reactogenicity was not different in both groups, the first Pa dose at birth leading to only few symptoms.

Pneumococcal vaccination:

(1635) Pneumococcal conjugate vaccines have been shown to reduce vaccine type invasive pneumococcal disease in immunized infants and to induce herd immunity in immunized populations. As the major global burden of pneumococcal morbidity is related to pneumonia, it is important to measure vaccine efficacy and effectiveness against pneumonia. These vaccines have been shown to reduce pneumonia as measured by a WHO consensus endpoint of consolidation on Xray. Clinical endpoints in randomized trials reveal vaccine efficacy against a greater burden of pneumonia than that defined strictly by a consolidated Xray. The vaccine demonstrates little efficacy against bronchiolitis, but prevents a significant fraction of lower respiratory tract infections associated with a CRP level >40mg/l. The vaccine also prevents pneumococcal superinfection of influenza, human metapneumovirus and other viral pneumonias. As the etiology of pneumonia is multifactorial, and little longitudinal surveillance of pneumonia exists, there are currently no reliable data on the effectiveness of conjugate vaccines in the prevention of pneumonia in immunized populations. Given the proven impact of conjugate vaccines on carriage of vaccine type pneumococi, it may be assumed that the observed reduction of the burden of pneumonia in the elderly is caused by the immunization of children. Conjugate pneumococcal vaccine has been shown to reduce the burden of pneumonia in HIV infected children. As the burden of pneumococcal disease is so great in these children, the vaccine attributable reduction of disease is greater among HIV infected children and may be greater in some parts of Africa, than in HIV uninfected children. Conjugate pneumococcal vaccine has been shown to reduce all cause mortality by 16% in rural parts of Africa.

(1636) Epidemiological analysis of pneumococcal middle ear isolates has failed to determine specific otitis serotypes or MLST sequence types. The apparent propensity for most or all non-vaccine pneumococcal serotypes to cause acute otitis media (AOM) contrasts AOM with invasive pneumococcal disease. Clinical trials and post marketing evaluation of pneumococcal conjugate vaccines have demonstrated efficacy for prevention of AOM in infants. A modest decline in episodes due to vaccine serotypes accompanied by a shift in microbiology (increase in episodes due to non-vaccine serotypes) have been reported. Non-vaccine serotypes are now recovered from a larger proportion of AOM cases in vaccinated children, and non-typable Haemophilus influenzae is the most common pathogen in children with AOM failing initial therapy. A decline in penicillin resistance among middle ear pathogens and a decrease in the frequency of treatment failure have also been reported, however a multidrug resistand type 19A is emerging as a significant cause of treatment failure. Preliminary data on two experimental vaccines also demonstrate efficacy against pneumococcal AOM in clinical trials (PncOMP) and inclusion of protein D as a conjugate (PHiD-CV) for prevention of disease due to non-typable Haemophilus influenzae and pneumococci is encouraging.

(G-129) Since the introduction of pneumococcal conjugate vaccination in the USA, a decrease of the relative frequency of pneumococci as the causative agent of acute maxillary sinusitis in children has been observed. Non-typable H. influenzae is now the most frequent pathogen (41%), followed by S. pneumoniae (21%), and M. catarrhalis (14%). 44% of H. influenzae were beta-lactamase positive.

(G-155) Also in adults with acute maxillary sinusitis, a significant shift of the causative pathogens occurred after the introduction of the vaccination of children with the 7-valent conjugate pneumococcal

vaccine. Haemophilus non-type b became the most prevalent pathogen with an increase of the relative frequency from 36% to 43%. The frequency of S. neumoniae dropped from 46% to 35%. Where as the frequency of Penicillin-resistant pneumococci fell from 41% to 29%, an increase of β-lactamase positive Haemophilus influenzae from 33% to 39% was observed.

(G-135) The introduction of pneumococcal conjugate vaccine in the USA lead to a switch in the prevalence of vaccine type and non-vaccine type strains, the frequency of non-vaccine serotypes in invasive pneumococcal disease increased from 43% to 71%, but at a lower prevalence (!). Especially serotype 19A (non vaccine type) showed a marked increase. In addition, non-vaccine type strains have acquired resistance at a rate proportional to the replacement process.

(G-150) Already before the introduction of the heptavalent pneumoccal conjugate vaccinaton in Spain, an increased rate of pneumococcal invasive and non-invasive disease caused by S. pneumoniae serotype 19A has been observed. These 19A strains showed no clonal relationship.

(G-346) Due to selective pressure of antimicrobial use, antibiotic resistant peumococci became common since 1999 (pre vaccination era) in the USA. Selective pressure of PCV7 vaccination is postulated to have led to the observed change in resistant serotypes since, with non-vaccine type 19A currently being the predominant antibiotic resistant strain. Addition of this serotype to future vaccines should be considered.

(G-347) In Massachusetts, a significant progressive increase in the proportion of childhood invasive pneumococcal disease (IPD) caused by serotype 19A has occurred during the last 4 years. No other non-vaccine serotype has demonstrated significant increase during the same observation period. 19A is now the most common serotype causing IPD. In addition, Ceftriaxon resistance has emerged among 19A isolates in 2005.

(G-151) Different pneumococcal carriage rates were observed in vaccinated (24%) versus non-vaccinated (42%), day care attending children in Spain. Since only 20% of the studied children were vaccinated, no changes in the global carriage rate were observed.

(G-614) A French surveillance during 4 years showed a decrease in the pneumococcal carriage rate in children with acute otitis media after PN7V basic plus booster vaccination. No increase in the staphylococcal carrier rate was observed.

(G-615) In Germany, the incidence of otitis media (only clinical, no bacteriological evaluation) in children <2 years old decreased by 5.2% in all children and by 8.7% by children with risk factors ($p<0.001$).

(G-152) The 7-valent conjugated pneumococcal vaccine showed excellent safety and reactogenicity pattern in >5'000 evaluated German children, which were concurrently vaccinated with hexavalent vaccines. These children showed slightly more fever than the children in the control group, which received a hexavalent vaccine only.

(G-149) A general pneumococcal polysaccharide vaccination program in persons >65 years in Cantabria (Spain) showed only limited and statistically not significant effects.

(G-142) Pneumococcal surface adhesin A (PsA) was identified as a membrane associated surface protein, which is highly conserved and present in all pneumococcal serotypes. Intranasal and intraperitoneal vaccination of mice with P4 peptide (93% sequence homology to PsA) resulted in reduced carriage and bacteremia after nasal exposition and intrapertitoneal infection with pneumococci.

(G-345) Antibiotic prescription patterns vary significantly during the different seasons, reaching the highest prescription rates during the cold months. Interestingly, this variation is reflected by a seasonal change of the prevalence of antibiotic-resistant S. pneumoniae in middle ear fluid isolates. The proportion of Penicillin non-susceptible and Erythromycin resistant isolates decreased significantly during the warm months. No seasonal variation in serotypes was observed. The authors suggest reduced fitness of antibiotic-resistant S. pneumonia as an explanation for the observed phenomenon.

Polio vaccination:

Children in Puerto Rico, which were vaccinated according to the EPI schedule (6, 10, and 14 weeks), showed lower neutralizing antibody seroconversion rates to poliovirus type 1 and 2 (85.8%, 86.2%), compared to children that were vaccinated according to the US schedule (2,4, and 6 months) (99.6%, 100%). In the EPI group, seroconversion rates were lower in infants with high maternal antibody levels. Other factors that could have influenced immunogenicity were the earlier start of vaccination, the shorter delay between vaccinations, and the earlier time of blood drawing in the EPI group (1 month after last dose).

Rotavirus vaccination:

(1268) Both new Rotavirus vaccines (RotaTeq® and Rotarix®), while quite different in their formulation, number of administrations given, and viral composition, are highly efficacious in preventing severe rotavirus disease. However, efficacy studies have not yet been carried out in sub-Saharan Africa or the Asian subcontinent where the biggest need for rotavirus vaccines exists.

After licensure of a simian rotavirus derived vaccine (Rotashield®), intussusceptions were found to be associated with vaccine administration. The nature of this association, the actual attributable risk from vaccination, and the relationship of the association to the age of the child at the time of administration are all important factors for this severe adverse event. Of note, both new vaccines were safe in very large phase III trials and were not associated with excess risk of intussusceptions in these studies.

(G-617) 2 doses of GSK's rotavirus vaccine offered sustained high protection rates of about 80% during an observation period of 2 years against severe Rotavirus gastroenteritis (RVGE) in more than 7,000 subjects vaccinated at age 2 and 4 months. Efficacy against hospitalization due to RVGE was 83%. The overall reduction rate for hospitalization due to any gastroenteritis was 39.3%.

(G-618) The attenuated, monovalent GSK rotavirus vaccine showed a heterotypic protection of 71.4% against RVGE caused by G2[P4] (antigens not contained in the vaccine) in more than 26,000 evaluated infants. The small number of observed G2[P4] cases may limit the validity of this observation.

Smallpox vaccination:

(G-612) Persons who were vaccinia vaccinated 25-60 years ago showed stronger positive reactions after intradermal injection of 0.1ml of heat inactivated vaccinia virus, higher production of γ-INF after incubation with inactivated vaccinia virus, and higher remaining levels of neutralizing antibodies compared to vaccinia-naïve persons. This indicates cellular immunity and a long-lived immunological memory against smallpox after previous vaccinia vaccination. Remaining immunity may lower disease severity.

Varicella vaccination:

(G-872) In Germany, neurological complications (cerebellitis 7.9%, febrile convulsions 7.6%, meningoencephalitis 5.7%, cerebral convulsions 2.3%, and syncope 1%) were the most frequent complications in children hospitalized due to varicella. They occurred in 1.5 per 10,000 varicella cases. Varicella associated death cases were seen in 9% of the hospitalizations due to varicella, 10% suffered from permanent or possibly permanent sequelae.

Disclaimer: this summary was prepared by Dr Daniel Desgrandchamps, who kindly agreed to share his own meeting notes. Its content is the result of a selection and may not be taken as the exact translation of what has been presented by the authors – which will have to await the corresponding peer-reviewed publications.