Autumn 2006

VACCINE RESOURCE LINE

A MONTHLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

All doses of the quadrivalent HPV vaccine safe and effective in HPV-naive and previously infected women

Villa et al. Immunologic responses following administration of a vaccine targeting human papillomavirus Types 6, 11, 16, and 18. Vaccine *2006;24(27-28):5571-83.*

All doses of the new quadrivalent vaccine against the human papillomavirus (HPV) tested to date have proven to be safe and effective in women who were both HPV-naive on vaccination as well as those who had been previously exposed to the virus. Furthermore, protection against the four HPV strains in the vaccine persisted out to at least 2.5 years after receiving the vaccine.

Dr. Luisa Villa, Ludwig Institute for Cancer Research, São Paulo, Brazil, and multicentre colleagues assessed the safety and immunogenicity of the quadrivalent HPV vaccine against HPV types 6, 11, 16 and 18, or one of two placebo formulations, in a total of 1106 young women. Participants were either HPV 6, 11, 16 or 18-naive at baseline or had already been infected with vaccine HPV types. They were randomized to receive either a 20/40/40/20 µg dose of the vaccine, a 40/40/40/20 µg dose of the same vaccine or an 80/80/40/80 µg dose of the vaccine or placebo. Recipients received the vaccine or placebo on day 1, month 2 and month 6 following study enrolment.

"For all three formulations, 100% of subjects seroconverted [i.e. showed evidence of vaccine-induced immune responses] by month 7," investigators reported, "and baseline vaccine-type HPV-naive subjects who received the 20/40/40/20 µg formulation of the quadrivalent vaccine mounted a robust immune response." As importantly—given the ubiquitous nature of HPV infection—women with detectable, vaccine-type anti-HPV levels prior to vaccination responded with faster rises, higher peaks and higher persistence levels of relevant HPV antibodies compared with HPV-naive women, study authors emphasized.

To assess long-term immunogenicity, the per cent of per-protocol participants who had seroconverted at month 7 were retested at months 18 and 36. "Among subjects who had valid immunoassay results, 98%, 98%, 100% and 86% were seropositive for HPV types 6, 11, 16 and 18 at month 18," researchers noted, while 94%, 96%, 100% and 76% remained seropositive for the four respective serotypes at month 36. Rates of systemic clinical adverse experiences were generally comparable across all treatment groups, the most commonly reported vaccine-related adverse events being headache and pyrexia.

"To our knowledge, this is the first report demonstrating that administration of a quadrivalent HPV vaccine to women with detectable HPV antibodies prior to vaccination results in an anamnestic [memory-immune] response," the authors stated, adding that based on their findings, "it is clear that the administration of the quadrivalent HPV vaccine confers protective efficacy for at least 2.5 years' post-vaccination."

The lowest dose of the vaccine tested in this study has been chosen for evaluation in ongoing phase II clinical trials.

Rotavirus remains major cause of diarrhea in hospitalized US children

Malek et al. Diarrhea- and rotavirus-associated hospitalizations among children less than 5 years of age: United States, 1997 and 2000. Pediatrics *2006;117(6):1887-92.*

Rotavirus remains the major cause of diarrhea among young children hospitalized for diarrhea in the US, according to an analysis of the Kids' Inpatient Database (KID), a national sample of 80% of pediatric hospital discharges from community hospitals in the US.

Dr. Mark A. Malek, Respiratory and Enteric Virus Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, and multicentre colleagues identified all hospital discharge records reporting diarrhea among children under the age of five for the years 1997 and 2000.

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"In 1997 and 2000, diarrhea was coded in 13% of all childhood hospitalizations, for an estimated cumulative incidence of one diarrhea hospitalization per 23 to 27 children by age 5," investigators reported.

The etiology of the diarrhea was not coded for approximately two-thirds of these hospitalizations. However, approximately one-third of them were coded as being viral in nature and rotavirus emerged as the most common recorded pathogen, accounting for 18% of all diarrhea-associated hospitalizations in 1997 and 19% of them in the year 2000. Investigators also observed that in the year 2000, the number of hospitalizations for diarrhea demonstrated a "clear winter peak" from December through April.

"Hospitalizations presumed to be non-infectious and of viral etiology—which together accounted for 95.5% of all diarrhea-associated hospitalizations—also exhibited the same winter seasonal pattern," they added. Only a small fraction of the hospitalizations were bacterial in origin and for these, investigators observed a small peak of hospitalizations between July and September.

"Our data demonstrate that diarrhea is associated with 150,000 to 170,000 hospitalizations annually… among US children," the authors noted, adding that "the promise of effective, safe rotavirus vaccines may provide the best opportunity [there is] to reduce the morbidity and associated direct and indirect economic burden attributable to severe diarrhea among US children."

Inhalation of pneumococcal vaccine induces comparable antibody responses to intramuscular injection in COPD patients

Meyer et al. Inhalative vaccination with pneumococcal polysaccharide in patients with chronic obstructive pulmonary disease. Vaccine *2006;24(31-32):5832-8.*

Inhalation of a pneumococcal polysaccharide vaccine can induce rapid serum antibody responses that are comparable to those induced with intramuscular (i.m.) injection in patients with chronic obstructive pulmonary disease (COPD), according to a multicentre trial.

Dr. Peter Meyer, Institute of Inhalation Biology and Asklepios Specialist Hospital, Pulmonology Department, Gauting, Germany, and colleagues evaluated the safety and efficacy of two routes of inhalative vaccination of the polysaccharide antigen in 30 COPD patients vs. that of standard i.m. immunization. "Every patient was vaccinated with a 0.5 mL of a 23-valent pneumococcal polysaccharide vaccine," investigators noted. However, the vaccine was deposited in the alveoli (alveolar vaccination) in one group and in the large airways (bronchial vaccination) in a second group. Results from these two routes of administration were then compared to those seen in the standard i.m. vaccination group. "Using an increase of the serum IgG antibody level by more than twofold as a definition of response to vaccination… the response rate was 7/10 in all study groups at 12 weeks," investigators indicated.

Indeed, mean antibody levels in responders at 12 weeks were 278 mg/L for those who received alveolar vaccination and 238 mg/L for those who received bronchial vaccination. The Mean serum antibody level for those who received standard i.m. injection was 737 mg/L but according to investigators, this level was not significantly higher when compared to individual or combined inhalative groups.

On the other hand, when investigators analyzed increases of serum antibody levels, responding patients in the inhalative groups showed an average 3.6-fold increase following vaccination compared with an average 11-fold increase seen in i.m. recipients at 12 weeks and this difference in response was significantly higher for the i.m. group. Systemic side effects did occur in the inhalation groups and included fatigue, headache, shivering and fever but no patient required any medical intervention because of adverse events and no patient withdrew from the study because of adverse events.

"Our data show that standard i.m. injection of the vaccine as well as alveolar and bronchial inhalative vaccination will induce more than twofold response in the majority [7/10] of patients in each group of COPD patients," the authors noted, adding that their results "warrant further studies into this strategy, which may be a useful alternative to i.m. injection."

Improved PPV coverage rates for current indications would prevent more invasive disease than expanding the same

Greene et al. Preventability of invasive pneumococcal disease and assessment of current polysaccharide vaccine recommendations for adults: United States, 2001-2003. Clin Infect Dis *2006;43(2):141-50.*

According to researchers, improved vaccine coverage rates among individuals for whom the pneumococcal polysaccharide vaccine (PPV) is already recommended would prevent more episodes of invasive pneumococcal disease (IPD) than expanding current indications. However, of the potentially new indications for PPV use explored by the group, lowering the recommended age for universal vaccination to 50 years would prevent the most IPD episodes.

Dr. Carolyn Greene, Centers for Disease Control and Prevention, Atlanta, Georgia, and colleagues carried out a multi-state case series study of incident cases of IPD to determine the proportion of cases that might have been prevented if all individuals for whom PPV is currently indicated had actually received the vaccine. During the study period, a total of 1951 cases of IPD were detected among individuals at participating surveillance sites. Of all case patients, 83% had at least one indication to receive the vaccine, only 38% of whom had actually been vaccinated. Of the 1558 patients who had an indication to receive the vaccine, 44% had at least one immunocompromising condition.

After taking into account vaccine efficacy in immunocompromised patients, investigators estimated that

21% of all cases of IPD might have been prevented if everyone adhered to current recommendations. In contrast, expanding PPV recommendations to include individuals who smoke, African-Americans or those who have asthma would have prevented only 0.3% to 2.5% of all IPD cases, while expanding recommendations to include those between the ages of 50 and 64 would have prevented only 5% to 7% of all cases of IPD.

"Most adults with IPD had a current PPV indication but remained unvaccinated at the time of infection," the authors summarized. "Increasing vaccination coverage among persons for whom PPV is already indicated would prevent a substantial number of IPD cases in the future."

Only minority of students would get MMR vaccine after mumps outbreak on campus

Hamilton-West K. Factors influencing MMR vaccination decisions following a mumps outbreak on a university campus. Vaccine *2006;24(24):5183-91.*

Only one-third of one sample of university students would take advantage of a free measles-mumps-rubella (MMR) vaccine following an outbreak of mumps on campus. Findings suggest that students' perception of the risk of the MMR vaccine is at great odds with its actual risk as published in the scientific literature.

Dr. Kate Hamilton-West, Department of Psychology, University of Kent, Canterbury, UK, carried out a questionnaire on vaccine attitudes following a mumps outbreak in early 2004. "Student and staff were invited by the university to receive the combined MMR vaccination at sessions run by the local Health Protection Unit on three consecutive days," she reported. The questionnaire was completed two weeks after the vaccine had been offered.

Out of 210 respondents, 58.1% said they had received the MMR vaccine in the past, while 41.9% indicated that they had not. When asked if they had taken advantage of the free MMR vaccine offered by the university after the mumps outbreak, 34% of the students indicated that they did while 66% indicated they had not. "Previous receipt of the MMR vaccine was not significantly associated with uptake of the vaccine," Dr. Hamilton-West observed. For example, 39% of the students who had not received the vaccine in the past opted to receive the vaccine when offered it by the university vs. 30% of students who had received the vaccine in the past. "It is evident that perceptions of risk vary widely," she suggested. For example, students indicated that they felt the risk of contracting either measles, mumps or rubella ranged anywhere from 0 to 100% if not immunized. They also perceived that the risk of contracting each infection would be 0 to 90% even if they were immunized. Similarly, perceived risk of side effects and complications from the vaccine ranged from 0 to 100% and the perceived severity of each disease, including side effects of the vaccine, ranged from very mild to very serious.

"Until now, the public health information relating to the MMR [vaccine] has been mainly aimed at parents of young children," Dr. Hamilton-West commented. "University students may not therefore have received sufficient information relating to the MMR vaccine [but] as more mumps outbreaks are reported in university settings, it becomes increasingly important to implement effective immunization programs. The results of this study suggest that perception of the MMR [vaccine] varies widely among university students and that interventions should address factors such as attitudes towards the vaccine, perceptions of peer expectations and perceptions of barrier to uptake."

Community-wide vaccine program induces long-term protection against invasive pneumococcal disease

Millar et al. Effect of community-wide conjugate pneumococcal vaccine use in infancy on nasopharyngeal carriage through 3 years of age: a cross-sectional study in a high-risk population. Clin Infect Dis *2006;43(1):8-15.*

According to US investigators, a community-wide program during which infants between the ages of six weeks and seven months receive a full course of the pneumococcal conjugate vaccine induces long-term protection against vaccine-type (VT) nasopharyngeal carriage in a population with a high burden of pneumococcal carriage and a high risk of invasive pneumococcal disease. At the same time, community-wide vaccination with the same pneumococcal vaccine increases the prevalence of carriage of serotypes not contained in the vaccine. As investigators pointed out, the duration of protection against carriage is of particular importance, because it is this that confers indirect protection against disease among non-immunized contacts.

Under lead author Dr. Eugene V. Millar, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, researchers analyzed nasopharyngeal specimens collected at least 12 months after infants had received the final booster dose of the pneumococcal conjugate vaccine at 12 to 15 months of age. Infants had previously received three doses of the vaccine two months apart. (The original trial from which the current carriage trial continued had randomized infants on two Native American reservations to either full vaccination with the pneumococcal conjugate vaccine (PnCRM7) or a Neisseria meningitidis group C protein conjugate vaccine (MnCC). There were 749 infants enrolled in the follow-up carriage analysis. "Of those who received four doses [of the vaccine], the median age at each vaccination was 2.1, 4.6, 6.9 and 12.5 months of age, and the mean time since last vaccination was 27 months," the authors noted.

Results indicated that the overall pneumococcal carriage rates at 63.9% in PnCRM7 recipients were similar to rates seen in MnCC controls at 60.5%. "However, the prevalence of VT carriage was lower among the 493 PnCRM7 recipients [10.3%] than among the control subjects [17.1%]," the investigators reported. Conversely, the prevalence of non-VT carriage was higher at 39.3% among PnCRM7 recipients than among the control cohort at 29.9%, they added. "This study documents that

protection against VT pneumococcal carriage induced by PnCRM7 vaccination during infancy extends well beyond the immediate vaccination period and persists until at least three years of age," the researchers stated.

But as they also observed, the prevalence of overall pneumococcal carriage in this particular study population at approximately 60% is two- to threefold higher than that of similarly-aged children in the general US population, as well as in Europe. For example, 28% of MnCC recipients in this study who were colonized carried VT pneumococci, for an absolute VT carriage rate of 17.1% in this control group. Thus, the study demonstrated that even at moderate levels of immunization coverage, the PnCRM7 vaccine could sustain reductions in carriage of VT pneumococci in populations with a high burden of invasive disease and early intense pneumococcal carriage, researchers concluded.

Shortening fever duration in patients with influenza A and B infections

Kawai et al. A comparison of the effectiveness of oseltamivir for the treatment of influenza A and influenza B: a Japanese multicentre study of the 2003-2004 and 2004 -2005 influenza seasons. Clin Infect Dis *2006;43(4):439-44.*

Treatment of patients with either influenza A or B infections with the oral neuraminidase inhibitor oseltamivir significantly shortens the duration of fever compared with those who do not receive anti-influenza treatment, although fevers still lasted significantly longer for patients with influenza B than for those with influenza A, according to a Japanese study.

Dr. Naoki Kawai, Japan Physicians Association, Tokyo, and colleagues analyzed symptom duration in1818 patients with influenza A and another 1485 patients with influenza B. Both groups received treatment with oseltamivir 75 mg for adults and children who weighed 37.5 kg or more and 2 mg/kg for children under 37 kg b.i.d. for five days. Patients were divided into four groups based on the time between onset of fever (37.5° C or higher) and the first dose of medication taken. They were also divided into four subgroups based on their age. Patients were asked to take their body temperature at least three times a day and record when it dropped below 37.5° C, at which point they were deemed afebrile.

For treated patients with influenza A, fever lasted 47.9 hours compared with 82.4 hours for those who received no anti-influenza medication. For treated patients with influenza B, fever lasted 65.4 hours compared with 78.3 hours for untreated patients with the same type of influenza. "Furthermore, the duration of fever from onset was significantly shorter for patients with influenza A than for those with influenza B in all age groups," researchers observed. The duration of fever from the first administration also tended to be shorter in patients who started taking medication 25 to 36 hours after onset for patients with both influenza A and B, they added.

"These results indicate that inhibiting the increase of infected cells in the host is important for quickly reducing symptoms and accelerating recovery from illness," investigators concluded, adding that in patients with influenza B, it might be necessary to develop a more suitable regimen when treating patients with oseltamivir. ❑

UPCOMING EVENTS

7th Canadian National Immunization Conference
December 3-6, 2006 / Winnipeg, Manitoba

Vaccine Forum Spring 2007
January 22-24, 2007 / Baltimore, Maryland

Miami 2007 Winter Symposium: Innate Immunity and Novel Vaccines
January 27-31, 2007 / Miami, Florida

41st National Immunization Conference
March 5-8, 2007 / Kansas City, Missouri

World Vaccine Congress Washington 2007
March 19-22, 2007 / Washington, DC

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