May/June 2009

VACCINE RESOURCE LINE

A BIMONTHLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

Avian flu vaccine shown to be safe, immunogenic in phase II study

Wu et al. Immunogenicity, safety, and cross-reactivity of an inactivated, adjuvanted, prototype pandemic influenza (H5N1) vaccine: a phase II, double-blind, randomized trial. Clin Infect Dis *2009;48(8):1087-95.*

An inactivated, aluminum adjuvanted, whole-virion H5N1(avian flu) vaccine has been shown to be safe and highly immunogenic in a phase II, double-blind trial. The vaccine also elicited significant cross-reactivity against heterologous H5N1 strains, according to the same study.

Dr. Jiang-Wu, Beijing Centers for Diseases Control and Prevention, China, and multicentre colleagues, reported the effects of dosage and regimen on the immunogenicity and safety of the vaccine as well as its potential for cross-reactivity. "From August 28 to December 22, 2007, 402 participants were enrolled from a group of clinically healthy volunteers aged 18 to 60," the authors reported. Some 301 participants were randomly assigned to receive two doses of 5, 10 or 15 ug of the vaccine 28 days apart, while the remaining 101 participants received two doses of 10 ug 14 days apart. All formulations were well tolerated, with most local and systemic reactions being mild to moderate in nature.

The highest immune response was elicited after recipients received two doses of the highest dose of the vaccine, with 90% and 100% seroconversion rates. Both the 10- and the 15-ug doses met or exceeded European Union licensure criteria. These criteria specify that the geometric mean ratio exceed 2.5, that the seroconversion rate exceed 40% and that the seroprotection rate exceed 70% of H1 antibody. As the authors indicated, immune responses were higher when participants received vaccine doses 28 days apart. Nevertheless, "receipt of vaccine on days 0 and 14 can induce satisfactory immune response in a shorter interval… which would be the preferred choice for immunologically-naïve persons who are about to encounter the H5N1 virus," they stated.

The World Health Organization is currently encouraging investigation into antigen-sparing strategies—including the use of adjuvants and whole-virion vaccines—as during a pandemic, the demand for vaccines will outpace capacity to manufacture them.

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Quadrivalent HPV vaccine proves highly effective against vaccine-type disease in older, HPV-free women

Muñoz et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24-45 years: a randomised, double-blind trial. Lancet *2009;373:1949-57.*

The quadrivalent human papillomavirus (HPV) vaccine has proven to be 90.5% effective against disease or infection related to HPV 6, 11, 16 and 18, and 83.1% effective against disease or infection related to HPV 16 and 18 alone in a cohort of older women with no history of genital warts or cervical disease on study entry.

Dr. Nubia Muñoz, National Institute of Cancer, Bogota, Colombia, and multicentre colleagues enrolled women between the ages of 24 and 45 from a variety of community and academic health centres into an ongoing, multicentre, randomized, placebo-controlled double-blind study. "Participants were allocated by computer-generated schedule to receive quadrivalent HPV vaccine (n=1911) or placebo (n=1908) at day 1, and months 2 and 6," investigators reported. The coprimary end points were the combined incidence of infection of at least six months' duration and cervical and external genital disease. The secondary efficacy end point was the combined incidence of infection related to HPV 6 or 11 of six months' or more duration and cervical and external genital disease.

Approximately one-third of women were positive to HPV 6, 11, 16 or 18 at baseline by serological or DNA testing, but, as researchers pointed out, only 7.9% were infected with vaccine HPV type at baseline as determined by DNA testing alone.

"Almost all women had had sexual intercourse before enrolment and the mean age of first sexual experience was 19 years," the authors noted. In the per-protocol efficacy population, the vaccine proved to be 92.6% effective in the prevention of vaccine-type-related infection alone and 92.4% effective against cervical intraepithelial neoplasia and external genital lesions. Since infection and disease were present at baseline, efficacy in the intention-to-treat population was predictably lower: 30.9% effective against the first coprimary end point and 22.6% effective against the second coprimary end point.

Interestingly, compared with women between the ages of 16 and 23 who were enrolled in the quadrivalent HPV program, "We noted that the antibody responses in women aged 25 to 45 years were comparable for HPV 16 and slightly lower for HPV 6, 11 and 18," the authors stated. Importantly, almost all of the women in this older-aged cohort seroconverted, with between 97% and 99% of the women being anti-HPV seropositive to one of the four vaccine types.

There were no reported vaccine-related serious adverse events in either population, the authors observed, who concluded that their results "are generalisable to women aged 24 to 45 years in the general population who have had no recent cervical disease and no previous history of external genital disease."

Changes in rotavirus activity following vaccine introduction

Parashar UD, Glass RI. Rotavirus vaccines—early success, remaining questions. N Engl J Med *2009;360(11):1063-5.*

"Remarkable" changes have been seen in rotavirus (RV) activity in the US in 2008, as reflected in data presented at the annual joint meeting of the Infectious Diseases Society of America and the Interscience Conference on Antimicrobial Agents and Chemotherapy in October 2008.

As detailed by Dr. Umesh Parashar, Centers for Disease Control and Prevention, Atlanta, Georgia, and Dr. Roger Glass, National Institutes of Health, Bethesda, Maryland, data from a national network of sentinel laboratories in the US demonstrated that the onset and peak of the 2008 RV season were delayed by 15 and eight weeks, respectively, compared with the six consecutive seasons preceding the introduction of the first new vaccine. "Furthermore," Dr. Parashar noted, "in 2008, the number of positive RV tests decreased by 67% as compared with 2000 and 2006, and the proportion of all RV tests performed in 2008 that were positive was 69% lower than the median proportion during the RV seasons from 2000 through 2006."

These changes were greater than what were expected based on the estimated coverage of the RV vaccine in the US, he added, including a change among children over the age of three who would have been too old to be eligible for vaccination in 2007 and 2008. Findings suggest that the vaccine is conferring indirect benefits to unvaccinated individuals, presumably through herd immunity. Reassuringly, adverse event monitoring out to two years post-licensure do not indicate that the vaccine is associated with any risk of intussusception, although continued monitoring is necessary to completely assess its safety. Dr. Parashar also pointed to the "high level of compliance" with the recommendation that the RV vaccine not be given after 14 weeks of age, with 86% to 93% of first doses in the US being given between 6 and 12 weeks of age.

Whether or not the RV vaccines will work as well in the developing world is still not known. However, the Global Alliance for Vaccines and Immunization has already approved financial support for the purchase of RV vaccines for eligible countries in Latin America and Europe, where vaccine efficacy has been proven.

"With financial support and recommendations from the World Health Organization and other international health organizations, the long wait for safe and effective vaccines to prevent deaths and severe disease from RV diarrhea among children in the developing world may soon be over," Dr. Parashar stated.

HPV vaccine risk minimal, no serious effects seen to date

Borja-Hart et al. Human papillomavirus vaccine safety in pediatric patients: An evaluation of the Vaccine Adverse Event Reporting System. Ann Pharmacother *2009;43:356-9.*

Since the introduction of the human papillomavirus (HPV) vaccine, an estimated 16 million doses have been distributed in the US and 26 million doses worldwide. The risks associated with the HPV vaccine appear to be minimal compared with infection from the virus itself and no causality has been established between existing reports and any serious adverse events (AEs).

Nancy Borja-Hart, PharmD, Assistant Professor, Nova Southeastern University, Fort Lauderdale, Florida, and colleagues evaluated the occurrence of HPV vaccine-related AEs in the pediatric population as reported by the media based on the safety data and postmarketing surveillance in the Vaccine Adverse Event Report System (VAERS) database.

VAERS is a passive reporting system that allows any person to report any AE seen in association with vaccination. It showed a total of 3174 AEs that had occurred in children and adolescents from the time it was approved in the US to June 2008. "A total of three deaths have been reported to the VAERS database," the authors added. One was due to diabetic ketoacidosis, another due to acute respiratory distress and the third to suspected long QT interval. According to the VAERS report, none of these cases appeared to be related to the HPV vaccine. Other AEs documented in the VAERS database during the same interval included deep vein thrombosis (two); Guillain-Barré syndrome (thirteen); paralysis (nine); pulmonary embolism (one); stroke (three); and seizures (twenty).

"Postmarketing surveillance is crucial in the pharmaceutical industry to determine the occurrence of AEs not fully elucidated in premarketing clinical trials," the authors stated, "but patients

concerned about AEs reported in the media should be reminded that a definitive relationship between the vaccine and the AEs has not been established."

Stem-cell transplant recipients and pneumococcal vaccine recommendations: Final results of the IDWP01 trial

Cordonnier et al. Randomized study of early versus late immunization with pneumococcal conjugate vaccine after allogeneic stem cell transplantation. Clin Infect Dis *2009; 48(10):1392-401.*

According to final results of the European Group for Blood and Marrow Transplantation (EBMT) IDWP01 trial, allogeneic stem cell transplant (SCT) recipients should receive the 7-valent pneumococcal conjugate vaccine three months after undergoing SCT and a dose of the 23-valent polysaccharide pneumococcal vaccine at 12 months for enhanced immunogenicity.

Dr. Catherine Cordonnier, Professor of Hematology, Hôpital Henri Mondor, Créteil, France, presented further analyses of the IDWP01 trial during the 2009 annual meeting of the EBMT (Abstract 323). In the study, responses to pneumococcal immunization were compared between those who received the 7-valent conjugate vaccine early (at three months) as opposed to late (at nine months). Results showed that responses to three doses of the vaccine given at one-month intervals were not inferior among those who received the vaccine early compared with those who received the vaccine late.

In a continuation of the same study, investigators analyzed responses to one dose of the 23-valent polysaccharide pneumococcal vaccine given either at 12 months in the early group, or at 18 months in the late group. A total of 158 SCT recipients were included in the trial. Current analyses reassured investigators that firstly, there was no difference in antibody levels as measured by ELISA and geometric mean opsonophagocytic (OPA) titres between early and late responders. "We also saw a significant relationship between ELISA and OPA titres for the seven antigens of the conjugate vaccine, which is an important point," Dr. Cordonnier observed, "as there is no consensus about what an OPA protective titre is." Investigators also examined whether the 23-valent polysaccharide vaccine had a booster effect on serotypes specific to the conjugate vaccine as well as the effect it had on serotypes pn1 and pn5 contained only in the polysaccharide vaccine. Antibody testing prior to delivery of the 23-valent polysaccharide vaccine indicated that 36 patients were non-responders to the conjugate vaccine. Following a boost with the polysaccharide vaccine, "Twenty-one patients remained non-responders," Dr. Cordonnier reported, "but the other 15 patients (42%) responded to the polysaccharide boost."

Regarding the effect of the polysaccaride vaccine on pn1 and pn5 serotypes, the geometric mean concentrations were significantly lower at one month in the early group compared to the late group. Conversely, the difference in the geometric mean concentrations did not affect the per cent of patients who responded to the polysaccharide boost at either one month or two years, with 80% of the early group having a significant response to the pn1 antigen vs. 87% in the late group, and 84% of the early group responding to the pn5 antigen vs. 94% of the late group.

"Our conclusion to this part of the analysis is that one dose of the 23-valent polysaccaride vaccine after three doses of the conjugate vaccine extends the serotype coverage to additional antigens not included in the conjugate vaccine, and it also increases the response rate to the serotypes included in the conjugate," Dr. Cordonnier observed, "and the recommendation is now to consider the polysaccharide vaccine at 12 months." Expanding further on what will be recommended in new international guidelines for SCT recipients, Dr. Cordonnier re-emphasized that SCT recipients should receive three doses of the conjugate vaccine, starting within three and six months of undergoing SCT, at one- to two-month intervals followed by either one dose of the 23-valent polysaccharide vaccine at 12 months. In the case of chronic graft-vs.-host disease, a fourth dose of the conjugate vaccine may be considered as it is probably more effective in patients with GVHD, she added. A booster with the 7-valent conjugate vaccine may also be given at two years as antibody titres may be waning at two years and the vaccine has proven to be safe in SCT patients.

Dose-sparing intradermal influenza vaccination option for immunocompromised patients

Gelinck et al. Intradermal influenza vaccination in immunocompromized patients is immunogenic and feasible. Vaccine *2009;27(18):2469-74.*

Dose-sparing intradermal influenza vaccination is a feasible alternative to routine intramuscular (i.m.) vaccination in immunocompromised patients including individuals receiving treatment with anti-tumour necrosis factor (TNF) agents, HIV-infected patients and patients who have undergone hematologic stem cell transplantation (HSCT).

Dr. Luc B.S. Gelinck, Erasmus Medical Center, Rotterdam, The Netherlands, and multicentre colleagues randomized 156 immunocompromised patients and 41 healthy controls to either intradermal influenza vaccination using one-fifth of the i.m. dose or to standard i.m. vaccination. Participants received either 0.5 mL of the 2005/2006 trivalent influenza vaccine given i.m. or 0.1 mL of the same vaccine given intradermally. "All study subjects were vaccinated in the fall and winter of 2005 with a commercially available trivalent subunit influenza vaccine," investigators noted. The primary outcome included geometric mean titres and protection rates.

Results indicated that intradermal vaccination induced similar postvaccination titres compared to standard i.m. vaccination in all four study groups. "Healthy controls showed

the best responses, followed by the anti-TNF group, the HIV group and the HSCT group, respectively," the authors indicated. Higher prevaccination titres were also associated with higher postvaccination titres in all study groups. Indeed, "remarkably high" postvaccination protection rates following intradermal vaccination were observed in a subset of severely immunocompromised patients who had been vaccinated before, investigators observed.

Of further interest was the development of local skin reactions following intradermal vaccination. While immunocompromised patients developed milder local skin reactions than healthy controls, "The occurrence of a local skin reaction after intradermal vaccination is predictive of a response to at least one of the vaccine antigens," they added. Intradermal vaccination is of particular interest for immunocompromised patients because the dermis has a network of antigen-presenting cells which provide an optimal environment to deliver a vaccine. The favourable immunologic properties of the dermis allow for smaller quantities of a vaccine to be delivered as well.

Acceptance of HPV vaccination high among Italian mothers even though knowledge of HPV was low

Tozzi et al. Attitudes towards HPV immunization of Italian mothers of adolescent girls and potential role of health professionals in the immunization program. Vaccine *2009;27(19):2625-9.*

Acceptance of vaccination against the human papillomavirus (HPV) was found to be high among a large group of Italian mothers, the majority of whom indicated they would have their daughters vaccinated even though they had poor knowledge of HPV infection.

Dr. Alberta Tozzi, Bambino Gesù Hospital, Rome, Italy, and colleagues carried out a cross-sectional study on a large sample of mothers of adolescent girls in late 2007. Earlier in the spring of 2007, the Ministry of Health started an information campaign regarding HPV infection and HPV vaccination was offered to adolescent girls born in 1997 early in 2008. "Aims of the study were to assess parents' knowledge about HPV and HPV vaccination and their willingness to have their daughters immunized," investigators observed.

A total of 807 mothers completed the telephone interview. Investigators found that at least one-third of the mothers had never heard about HPV infection and only one-quarter of them felt they had sufficient information about it. Of those who knew about HPV, over 60% of them indicated that they knew about it through the national HPV immunization campaign.

Despite their modest understanding about HPV, "The proportion of mothers willing to accept HPV immunization for their daughters was close to 85% and cost did not represent a barrier to vaccination since nearly the same proportion of them reported to be ready to pay for having their daughters vaccinated," the authors noted. Fewer than 10% of the sample felt that HPV vaccination would encourage sexual promiscuity, they added.

Immunizations are not usually provided by pediatricians in Italy, yet over 76% of the mothers interviewed felt that they would prefer a pediatrician to immunize their daughters. "Our findings suggest that improving parents' knowledge [about HPV] may not increase vaccine acceptability," the authors noted, "and that acceptance of HPV immunization is expected to be high in our country." ❑

UPCOMING EVENTS

86th Annual Meeting of the Canadian Pediatric Society
June 23-27, 2009 / Ottawa, Ontario

18th International Society for Sexually Transmitted Diseases Research
June 28-July 1, 2009 / London, UK

8th Annual Public Health Systems Research Interest Group Meeting
June 30-July 1, 2009 / Chicago, Illinois

4th Europediatrics 2009
July 3-6, 2009 / Nottingham, UK

International Conference on Circumpolar Health
July 11-16, 2009 / Yellowknife, Northwest Territories

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