Winter 2006

VACCINE RESOURCE LINE

A MONTHLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

Few medically attended events observed following influenza vaccination in young children

Hambidge et al. Safety of trivalent inactivated influenza vaccine in children 6 to 23 months old. JAMA *2006;296(16):1990-7.*

Very few medically attended events, none of them serious, were observed following administration of the trivalent inactivated influenza vaccine in children between the ages of six and 23 months, according to the largest population-based study to date evaluating the safety of the vaccine.

Dr. Simon Hambidge, Kaiser Permanente Colorado, Denver, and multicentre colleagues conducted a retrospective chart review looking for significant, medically attended events following administration of the trivalent inactivated influenza vaccine to young children. "Our primary outcome measure was any medically attended event associated with the trivalent inactivated influenza vaccine in a 14-day risk window after vaccination when compared with two control periods, one before and one after vaccination," study authors explained.

A total of 45,356 children between the ages of six and 23 months received 69,391 influenza vaccinations between 1991 and 2003. Slightly over one-third of them had a medical condition that could put them at higher risk of complications from influenza infection and the remainder were healthy children. On first analysis, it appeared that gastritis or duodenitis was more likely to occur during the risk window, but further analyses showed that neither condition was significantly associated with vaccination. A recent report to the Vaccine Adverse Events Reporting System suggested there may have been a signal for febrile seizures in young children three days after receiving the trivalent inactivated influenza vaccine. Examining this in more detail, investigators again did not see any signal for convulsions in the three-day risk window, nor did they see any increased risk of Guillan Barré or oculorespiratory syndrome.

"We conducted a population-based study using large linked databases to examine the safety of the trivalent inactive influenza vaccine in young children 6 to 23 months old," investigators reported, "and our study adds to prior evidence that the influenza vaccine is safe in infants and young children."

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Sustained long-term efficacy observed for quadrivalent HPV vaccine out to five years

Villa et al. High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. Br J Cancer *2006;95(11):1459-66.*

Sustained long-term efficacy and immunogenicity has been observed out to five years in young women who received three doses of the quadrivalent human papillomavirus (HPV) vaccine during the original three-year, randomized trial of the vaccine vs. placebo.

In what is the longest efficacy evaluation to date of the quadrivalent vaccine, Dr. Luisa L. Villa, Ludwig Institute for Cancer Research, Sao Paulo, Brazil, and multicentre colleagues followed a subset of 241 participants who underwent a further two years of follow-up at the end of the original trial. In the original trial, a total of 1158 women between the ages of 16 to 23 were randomized to receive either three doses of the quadrivalent vaccine containing HPV 6, 11, 16, and 18 virus-like particles or placebo.

"At five years' post-enrolment, the combined incidence of HPV 6/11/16/18-related persistent infection or disease was reduced in vaccine recipients by 96% [two cases on vaccine vs. 46 on placebo]," the authors reported. There were no cases of HPV 6/11/16/18-related precancerous cervical dysplasia or genital warts in vaccine recipients and six cases in placebo recipients.

High efficacy over the two-year extension was also observed when investigators considered only study data from per-protocol participants who were eventually enrolled in the extension phase. Among this cohort, there was only one case of HPV infection among vaccine recipients, which was detected at months 12 and 18 only, vs. 22 cases of persistent infection or disease in placebo controls.

Investigators also analyzed results in a modified intention-to-treat (MITT) population that included all participants who were naive to the relevant HPV vaccine subtypes on enrolment and who had received at least one dose of the vaccine or placebo. "The observed efficacy against infection [in the MITT group] was 93.5%," investigators reported. "No cervical, vulvar or vaginal disease or genital warts due to HPV 6, 11, 16 or 18 was observed in quadrivalent vaccine recipients [efficacy=100%]." As the authors discussed, phase III studies carried out in over 18,000 women have shown that the quadrivalent vaccine is 100% effective against cervical, vaginal and vulvar precancerous lesions and genital warts through two years of follow-up. Results from the current extension study confirm that there were no

breakthrough cases of disease over the full five-year study, suggesting that the quadrivalent HPV vaccine remains highly immunogenic through five years.

"All sexually-active individuals are at risk for HPV infection and disease, including those who do not engage in penetrative sexual intercourse," investigators observed. "Vaccination of adolescents and young adults… is expected to greatly reduce the burden of cervical and other anogenital cancers, low- and high-grade intraepithelial neoplasias and genital warts."

Hepatitis A vaccine immunogenic in infants as young as 12 months of age

Guerra et al. Safety, tolerability and immunogenicity of VAQTA given concomitantly versus nonconcomitantly with other pediatric vaccines in healthy 12-month-old children.
Pediatr Infect Dis J *2006;25(10):912-9.*

The hepatitis A vaccine is highly immunogenic and well tolerated when given to infants as young as 12 months of age regardless of initial hepatitis A serostatus, American researchers reported. The vaccine can also be safely given concomitantly with the measles-mumps-rubella (MMR) vaccine as well as with other recommended pediatric vaccines. Dr. Fernando Guerra, San Antonio Metropolitan Health District, Texas, and multicentre colleagues enrolled 617 children 12 months of age into the study, some 503 of whom completed it. All children received dose 1 of hepatitis A vaccine at visit 1 and dose 2 at visit 3, investigators reported. An active study control group was used to compare responses to the vaccine after each dose. The vaccines administered in the study were routinely in use at the time the study was undertaken.

The first dose of the hepatitis A vaccine was given either alone or with the MMR vaccine and the varicella vaccine, while the second dose was given either alone or together with the diphtheria-tetanus-acellular pertussis vaccine (DTaP) and, optionally, with the oral or inactivated poliovirus vaccine. "Participants were followed for clinical adverse experiences and serologic responses to all vaccine antigens [were measured]," investigators noted, "Antibody responses were compared with historical controls for some indices."

The observed seropositivity rate for hepatitis A antibody after one dose of the vaccine given alone to initially seronegative infants was 98.3% while it was 100% after infants received the second dose. Given alone, seropositivity rates to the hepatitis A vaccine were similar to historical control rates of 99% in children between the ages of two and three years. The geometric mean antibody titres four and six weeks after receiving the second dose of the hepatitis were also similar for children who were initially seropositive as they were for children who were initially seronegative, investigators added.

Given concomitantly with the MMR and the varicella vaccines, seropositivity rates after the first dose of the hepatitis A vaccine were comparable at approximately 96%. When administered with the MMR vaccine, seropositivity rates to hepatitis A were over 89% and were similar to historical rates of 99% for each antigen. Given together with the varicella vaccine, however, varicella antibody rates of 79% were not as high as the historical rate of 90%. Seropositivity rates for hepatitis A after the second dose also reached 100% when the vaccine was given together with the DTaP and the poliovirus vaccine and were similar to historical rates.

Rates of adverse events were generally similar among all treatment groups. As researchers noted, it has been previously reported that children with transplacentally-acquired material antibody to hepatitis A have a poor response to the hepatitis A vaccine in the first year of life.

"In our study, children with hepatitis A antibodies present at the time of vaccination had geometric mean titres after doses 1 and 2 similar to those of children without initial detectable hepatitis A antibody," researchers reported, thereby suggesting that the presence of maternal antibodies at 12 months of age does not adversely affect immunogenic response to the hepatitis A vaccine.

Regular booster vaccinations needed throughout life to maintain immune responses in old age

Kaml et al. Booster vaccination in the elderly: their success depends on the vaccine type applied earlier in life as well as on pre-vaccination antibody titers. Vaccine *2006;24(47-48):6808-11.*

Regular booster vaccinations are needed throughout life to maintain responses to recall antigens in old age, according to European investigators. Dr. Maria Kaml, Austrian Academy of Sciences, Innsbruck, and multicentre colleagues analyzed how pre-vaccination antibody concentrations affected the magnitude of humoral immune responses to booster vaccination with a multivalent vaccine containing tetanus, diphtheria, pertussis and polio antigens in 252 healthy elderly volunteers. Antibody concentrations were measured prior to the booster shot and five weeks after. A small cohort of young individuals, median age 24, were used as controls. "Primary immunizations dated back many years in all participants and each participant had received regular booster injections since primary immunization," investigators remarked.

Analyses showed that antibody concentrations prior to vaccination were lower in the elderly cohort than in young controls for tetanus, diphtheria and two of the four pertussis antigens present in the vaccine, but were similar for one of the polio strains and for the other two pertussis components. Five weeks after vaccination, most of the elderly cohort had an elevated humoral antibody concentration to components of the vaccine, although they were still lower than those in younger controls for diphtheria and most of the pertussis components as well as to one of the polio strains.

At the same time, investigators noted that the magnitude of the antibody responses observed in the elderly cohort were greatly affected by pre-vaccination antibody titres for all components of the vaccine. In fact, if pre-vaccination antibodies were either low or absent, the elderly frequently could not mount a sufficient humoral response, especially against certain components of diphtheria and pertussis.

In contrast, pre-vaccination antibody concentrations against polio antigens were well above protective levels for most elderly participants and high post-vaccination antibody concentrations against all three polio strains were also observed in virtually all elderly participants. "These results demonstrate that protection over decades and a good booster effect after a long time can be expected when a live vaccine is used in the first place," investigators stated, "while regular boosting is particularly important when inactive compounds are used."

In Austria, health authorities recommend that individuals over the age of 60 be vaccinated against tetanus, diphtheria and pertussis every five years and against polio every 10 years.

Knowledge of chickenpox fatality may prompt parental acceptance of the Varicella vaccine

Scheifele et al. Seven fatal varicella infections in children were potentially avoidable: A report from IMPACT *centres from 2000 to 2005.* Paediatr Child Health *2006;11(7):413-415.*

Knowing that healthy children can die of chickenpox may prompt parents to accept the now recommended varicella vaccine available in Canada since the year 2000.

Dr. David Scheifele, Immunization Monitoring Program Active (IMPACT), Division of Infectious and Immunological Diseases, University of British Columbia, Vancouver, and colleagues documented seven fatal varicella infections in Canadian children between 2000 and 2005. During the same interval, the 12 Canadian pediatric referral centres that comprise the IMPACT surveillance network also tabulated 1900 varicella-related hospital admissions. "With the exception of one child, all of the children were thought to have normal immune function," IMPACT members commented, although five of the children older than one year of age did have a chronic health problem. As IMPACT authors noted, those children with health problems who died of varicella infection were most likely in frequent contact with health professionals. "Despite this… none of the children received the varicella-zoster [VZ] vaccine," they observed.

Two children who died of varicella-related infections were too young to immunize; however, they would have been spared if susceptible older household members had received the vaccine instead of developing chickenpox, they added. As Dr. Scheifele and colleagues noted, all seven deaths occurred prior to routine implementation of the VZ vaccine in the home province. "Thus, although VZ vaccine was available, a lack of public funding limited uptake."

Some physicians apparently have been slow to accept the varicella vaccine for a variety of reasons. This is in spite of the fact that the vaccine has "an excellent safety record," even when administered concurrently with the measles-mumps-rubella vaccine, the authors observed. Protection against varicella infection is also long-lasting and vaccinated recipients have a "substantially reduced risk of zoster, which occurs in a mild form with minimal neuralgia," IMPACT authors noted.

By improving varicella coverage rates, investigators also predict that infection rates among children will approach that of measles, once as common as varicella but which have not caused a single death in Canada in the past decade, and are only rarely a cause of hospital admissions. "For those who consider chickenpox a benign illness, we have described seven reasons to reconsider that view," investigators concluded. "Prevention through vaccination is the better approach."

Sixth dose of the tetanus-diphtheria-acellular pertussis vaccine acceptably safe and well tolerated in adolescents

Zepp et al. Safety of reduced-antigen-content tetanus-diphtheria-acellular pertussis vaccine in adolescents as a sixth consecutive dose of acellular pertussis-containing vaccine.
J Pediatr *2006;149(5):603-10.*

The classic signs of pertussis are often absent in adolescents and they may therefore be a source of infection for susceptible infants and other family members. According to a randomized, double-blind, crossover trial, a booster dose of a reduced antigen-content, tetanus-diphtheria-acellular pertussis (Tdap) vaccine is acceptably safe and well tolerated when given as a sixth consecutive dose to adolescents.

Dr. Fred Zepp, Children's Hospital, Johannes Gutenberg University, Mainz, Germany, and colleagues assessed the overall safety profile of the Tdap vaccine in adolescents who had been previously vaccinated with five consecutive doses of the diphtheria-tetanus-acellular pertussis (DTaP) vaccine at between four and six years of age. They also compared rates of local adverse events among those vaccinated with a sixth dose with adverse-event rates in the same adolescents after receiving a fifth dose. A total of 319 adolescents (mean age, 10.9 years) who had been previously vaccinated with either five doses of the DTaP vaccine or four doses of DTaP plus another acellular pertussis-containing vaccine received one dose each of Tdap and the hepatitis A vaccine.

A total of 144 who received the hepatitis A vaccine first followed by the Tdap vaccine were evaluable for safety as were 140 adolescents who received the TdaP vaccine first followed by the hepatitis A vaccine. After receiving the Tdap vaccine, over two-thirds of recipients reported pain and over half reported redness. Slightly over 40% also reported swelling while approximately 30% reported headache and 28% reported fatigue.

"The incidence of all pain, redness, swelling and increased arm circumference greater than 5 mm from baseline were statistically significantly higher after Tdap vaccinations than after hepatitis A vaccinations, with the exception of injection site pain that required medical attention and the incidence of increased arm circumference greater than 20 mm from baseline," investigators reported. Three of the 319 vaccination recipients did report an episode of large injection site swelling after Tdap vaccination but all resolved without sequelae.

Interestingly, 22 of the 48 adolescents who reported a large injection site swelling after their fifth dose of the pertussis-containing vaccine were given a sixth dose of Tdap and none reported a large injection site swelling after the sixth dose. Among adolescents who received five consecutive doses of DTaP and a sixth dose of Tdap, the incidence of redness and severe swelling 50 mm or greater also decreased from that reported after the fifth dose. "We speculate that the reported lower rates of the objective signs of swelling and redness are secondly to the lower antigen content in the Tdap vaccine used in this study than in the childhood-based DTaP vaccine," the authors observed.

In the US, prelicensure Tdap vaccine clinical trials did not include individuals who had previously received an acellular pertussis-containing vaccine schedule because DTaP vaccines were not routinely recommended for all five doses of the childhood DTaP schedule. Thus, the current study is the first to describe reactogenicity in the first available group of adolescents to be vaccinated with a sixth consecutive dose of the acellular pertussis vaccine, the majority of whom also received five doses of DTaP. Given that immunity wanes after pertussis vaccination early in life, booster vaccination with a single dose of acellular pertussis is now routinely recommended in adolescents in countries such as Canada.

No evidence of lesser immune response to meningococcal vaccine in infants compared with toddlers

Vu et al. Effectiveness analyses may underestimate protection of infants after group C meningococcal immunizations.
J Infect Dis *2006;194(2):231-7.*

No evidence of a lesser immune response to the Group C meningococcal vaccine has been detected in children immunized as infants compared with responses seen in toddlers, according to a multicentre study. Dr. David Vu, Children's Hospital Oakland Research Institute, California, and colleagues in the UK measured meningococcal antibodies in serum samples obtained from children between three and five years of age who were immunized with the group C meningococcal conjugate vaccine two to three years earlier when they were infants or toddlers. All of the immunized infants had received three doses of the vaccine. Findings were then compared to serum antibody levels from samples that had been obtained from children of comparable age prior to the introduction of meningococcal immunization.

Assay analyses showed that geometric mean serum antibody concentrations were higher at 0.82 µg/mL in immunized infants and 0.56 µg/mL in immunized toddlers than in unimmunized

historic controls at 0.08 µg/mL. Serum bactericidal titres ≥1:4—considered to be protective against meningococcal infection, authors observed—were higher in immunized infants (61%) than in immunized toddlers (24%) as was the geometric mean titre.

However, when investigators assessed passive protective activity, they found that half of the samples from immunized infants and 41% of those from immunized toddlers were protected against group C bacteremia, compared with 3% of unimmunized historic controls. As the authors discussed, the UK was the first country to introduce routine immunization with group C meningococcal conjugate vaccines. "During the first year after immunization, vaccine effectiveness was estimated to be high in all age groups," they observed. One to four years after being immunized, however, vaccine effectiveness dropped to essentially 0% in immunized infants and to 61% in immunized toddlers, although it remained high at 90% in immunized teenagers.

"In the present study, we evaluated persistence of serum group C antibodies two to three years after routine immunization of infants given the triple-dose schedule and of toddlers given the catch-up single-dose schedule," investigators explained. "On the basis of three different serologic assays, we can infer that vaccine effectiveness two to three years after immunization is either higher or not inferior in children given the accelerated triple-dose infant immunization schedule than in children given the single-dose toddler catch-up schedule."

Most high-risk Americans did not receive influenza vaccination during vaccine shortage

Brewer N, Hallman W. Subjective and objective risk as predictors of influenza vaccination during the vaccine shortage of 2004-2005. Clin Inf Dis *2006;43(11):1379-86.*

Most Americans at high objective risk for influenza infection, especially younger adults with chronic medical illnesses, did not receive the influenza vaccination in 2004 to 2005 when there was a shortage of the vaccine in the US.

Dr. Noel Brewer, University of North Carolina, Chapel Hill, and Dr. William Hallman, Rutgers University, New Brunswick, New Jersey, sought to identify the role of objective and subjective risk status in prompting participants to receive the vaccine during its rationing in the US. Out of 300 respondents, 63% were in one of the high-risk categories: 65 years of age and older; 18 to 64 years of age with high-risk health conditions; or individuals who had routine contact with high-risk individuals but no other risk factors. Analyses showed that fewer than one-third (31%) believed they were in a high-risk group, while one-third felt themselves to be at low risk despite being at high risk.

Overall, 25% of the group did receive the influenza vaccine between September 2004 and March 2005 and those who were at high objective risk (36%) were more likely to have been vaccinated than those at low objective risk, only 6% of whom also received the vaccine. People 65 years of age and older were also significantly more likely to have been vaccinated (66%) than younger adults with high-risk conditions (20%) and respondents in regular contact with high-risk individuals, 21% of whom also received the vaccine.

Conversely, people who believed they were at high risk for influenza infection were more likely than those who were actually at high risk to receive the vaccination, investigators observed. Other predictors of vaccine uptake were physician recommendation to be vaccinated, having had a prior flu shot, perceived effectiveness of the vaccine, belief that influenza vaccination does not cause influenza or severe adverse effects and perceived likelihood of getting influenza.

Some 24% of the group overall also indicated that the shortage of the vaccine discouraged them from being vaccinated, suggesting that "the mere announcement" of a vaccine shortage may discourage high-risk—not just low-risk—individuals from pursuing vaccination, study authors observed.

"Health communication efforts must be more effective in persuading adults with chronic illness and individuals in contact with persons at risk that they should be vaccinated against influenza," the authors concluded. "Health risk communication messages framed around readily identifiable risk factors, such as age, may be more effective in persuading people to get vaccinated than messages framed around the likelihood of getting ill or even the severity of the consequences." ❑

UPCOMING EVENTS

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

16th Annual Pediatric Infectious Diseases
February 7-10, 2007 / Banff, Alberta

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

2007 AMMI Canada-CACMID Annual Conference
March 14-18, 2007 / Halifax, Nova Scotia

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

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