March/April 2007

VACCINE RESOURCE LINE

A MONTHLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

Combination measles/mumps/rubella/varicella vaccine as safe and immunogenic as separate vaccines

Kuter et al. Safety and immunogenicity of a combination measles, mumps, rubella and varicella vaccine (ProQuad®). Hum Vaccin *2006;2(5):205-14.*

D'Angio et al. Measles-mumps-rubella and varicella vaccine responses in extremely preterm infants. Pediatrics *2007;119(3):e574-9.*

A single dose of the combined measles/mumps/rubella (MMR) and varicella vaccine given to infants between 12 and 23 months of age provokes the same magnitude of immune response as that achieved with separate administration of the MMR and varicella vaccines and is equally well tolerated.

Dr. Barbara Kuter, West Point, Pennsylvania, and multicentre colleagues detailed the combined safety and immunogenicity results from five separate trials evaluating the combination vaccine. A total of 5833 children, mean age 12.7 months, received a primary dose of the combination vaccine in studies 1 through 4, while a subset of these children (n=1395) received a second dose of the same combination vaccine three months after their first dose. Another 399 children, mean age 4.3 years, received the combination vaccine in study 5.

Comparing the antibody responses to all four antigens in the combination vaccine in each study to those achieved after a primary dose of the MMR vaccine as well as after the varicella vaccine, the latter two given concomitantly, confirmed that a single dose of the combination vaccine was highly immunogenic. Six weeks following vaccination with the combination vaccine, efficacy rates were over 95% against MMR and approximately 91% against varicella.

Study 4—designed to determine if the combination vaccine could be given together with other commonly used pediatric vaccines—also demonstrated that antibody responses to MMR, varicella, Hib, hepatitis B, diphtheria and tetanus were again similar between the concomitant group and the non-concomitant group and exceeded 95%, varicella again being slightly less effective at approximately 90% but similar between the concomitant and non-concomitant group.

At one year post-vaccination, high antibody titres against MMR and varicella persisted and were generally comparable to the persistence of antibodies following administration of the MMR and the varicella vaccines. For those infants who received a second dose of the combination vaccine three months after the first dose, response rates at six weeks remained above 98% for MMR, while responses to varicella increased to over 99% after the second dose. Response rates to all four antigens in the combination vaccine were comparable in older children as well. Fever and measles-like rash were the only vaccine-related systemic adverse experiences that were statistically more likely to occur in infants receiving the combination vaccine than when the two vaccines were given separately but they were largely mild and of short duration.

"The data from these five clinical trials conducted with [the combination vaccine] confirm that this new… vaccine is generally well tolerated and highly immunogenic in children 12 to 23 months of age and in children four to six years of age," investigators concluded. "As a combination vaccine for the prevention of four diseases, [the new vaccine] is expected to facilitate compliance with universal vaccination recommendations and to improve vaccination coverage of children against all four childhood diseases."

A separate study was carried out in which the immune responses of extremely preterm infants were evaluated following administration of the MMR and varicella vaccines. Thirty-two infants were evaluated, 16 of whom were born under 29 weeks' gestation and 16 of whom were term at birth. The group found that geometric mean titres (GMTs) at 15 months of age were similar between preterm and term children for all four antigens, findings which "support the prevailing recommendations for immunization of the preterm infant at the chronological age appropriate for a term infant."

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Oral rotavirus vaccine does not affect other parenteral pediatric vaccines

Rodriguez et al. Concomitant use of an oral live pentavalent human-bovine reassortant rotavirus vaccine with licensed parenteral pediatric vaccines in the United States. Pediatr Infect Dis J *2007;26(1):221-7.*

Concomitant administration of the oral pentavalent rotavirus vaccine does not influence either the safety or efficacy of other parenteral pediatric vaccines, according to the first study to evaluate its impact on antibody responses to other vaccines.

Dr. Zoe Rodriguez, Clinical Research Center, University of Puerto Rico School of Medicine, San Juan, and multicentre colleagues reported results from the Concomitant Use Study—a nested substudy within the REST (Rotavirus Efficacy and Safety Trial)—in which the immunogenicity and safety of the oral rotavirus vaccine was evaluated when given together with currently licensed pediatric vaccines in the US. All 1358 children in the Concomitant Use Study received three doses of the vaccine or placebo, as well as all prespecified licensed pediatric vaccines. Mean age at enrolment was 9.3 weeks for the oral rotavirus vaccine group and 9.4 weeks for the placebo group.

Overall, investigators found that 90% or more of infants in both groups developed antibody titres known to be protective against diphtheria, tetanus, polioviruses types 1, 2 and 3 and hepatitis B. Over 70% of both groups also developed protective antibody titres against Hib polyribosylribitol phosphate (PRP). "Pre-established criteria for demonstrating non-inferiority of antibody responses to hepatitis B surface antigen, Hib PRP, polio virus, diphtheria and tetanus in the [rotavirus] group compared with the placebo group were satisfied," investigators observed.

Antibody responses to the concomitant vaccines used in this study were similar between the two groups for 16 out of 17 of the antigens tested. The only difference in antibody titres between the rotavirus and placebo group was seen to those against pertactin, one of the components of the diphtheria/tetanus/acellular pertussis (DTaP) vaccine. However, investigators attributed this "outlying result" to the unusually high pertactin antibody titres in the placebo group as there was really no "biologically plausible" mechanism by which the oral rotavirus vaccine could interfere with antibody responses to this particular component of a parenteral vaccine.

Predictably, the rotavirus vaccine was found to be approximately 90% effective in preventing grade 1 to 4 rotavirus gastroenteritis of any severity, a result which was comparable to overall results seen in REST. There was a single case of intussusception in this nested study, as previously reported as part of the primary REST safety data.

"This study indicates that the addition of [the rotavirus] vaccine to the vaccination schedule will not likely change the expected safety profile of routine immunizations administered in the first six months of life," investigators concluded. "The totality of these immunogenicity, safety and efficacy data support concomitant administration of [the rotavirus] vaccine with DTaP, inactivated poliovirus, Hib, hepatitis B and pneumococcal conjugate-7 vaccines during the first six months of life."

Quadrivalent HPV vaccine highly effective in nine- to 15-year-old children

Reisinger et al. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: A randomized controlled trial.
Pediatr Infect Dis J *2007;26(3):201-9.*

As demonstrated in this double-blind trial, the quadrivalent human papillomavirus (HPV) vaccine is highly effective in nine- to 15-year-old boys and girls with antibody responses persisting through to at least one year following vaccination. Dr. Keith Reisinger, Primary Physicians Research, Pittsburgh, Pennsylvania, and multicentre colleagues randomized 1781 sexually-naive children to either the HPV vaccine containing types 6, 11, 16, and 18 L1 virus-like particles (VLPs) or saline placebo given on day 1 and again at months 2 and 6. "Serum-neutralizing anti-HPV 6/11/16 and 18 responses were summarized as GMTs and seroconversion rates," the authors explained, "and the immune response generated by a three-dose regimen of quadrivalent HPV vaccine was compared between boys and girls."

Results showed that for each of the four vaccine types, 99.5% or more of those in the per-protocol cohort had seroconverted one month after receiving three doses of the vaccine, regardless of gender. Indeed, the robustness of anti-HPV responses was highest in the youngest members of the cohort and overall, responses seen in the age group in this study were "substantially higher" than those observed in previous trials in which young women between the ages of 16 and 23 received the same vaccine. At month 18, one year after the preadolescents and adolescents in the current study had completed the vaccination regimen, 91.5% or more of vaccine recipients in the per-protocol population remained seropositive, regardless of gender. (In the earlier trial of 16- to 23-year-old women, the efficacy of the vaccine has persisted through to at least five years.) A significantly higher proportion of boys and girls in the vaccine group reported injection-site adverse reactions than placebo controls, but few recipients discontinued vaccination because of an adverse experience, investigators reported.

"The current study demonstrates that administration of quadrivalent HPV 6/11/16/18 L1 VLP vaccine to nine- to 15-year-old boys and girls is highly immunogenic, provides durable immunity through one year post-vaccination and is generally well tolerated," investigators concluded. "These results further support the implementation of a gender-neutral HPV vaccination program to eradicate cancers, precancerous lesions and genital warts caused by vaccine HPV types."

Higher-potency zoster vaccine well tolerated in recipients 50 years of age and older

Tyring et al. Safety and tolerability of a high-potency zoster vaccine in adults ≥50 years of age.
Vaccine *2007;25(10):1877-83.*

One dose of a higher potency zoster vaccine is generally as well tolerated as a lower potency dose in recipients ≥50 years of age. Dr. Stephen Tyring, University of Texas Health Science Center, Houston, and multicentre colleagues compared the safety and tolerability of two herpes zoster vaccine potencies in order to provide data on an expanded age group, notably adults ≥50. (The herpes zoster vaccine is currently approved for use in adults ≥60 years of age.)

The dose of the higher-potency vaccine tested was 207,000 plaque-forming units (PFU/0.65-mL dose) while the lower potency dose was similar to vaccine potencies studied in the SPS (Shingles Prevention Study) at approximately 58,000 PFU/0.65-mL dose. "Of primary interest were the incidences of vaccine-related serious clinical adverse events [AEs] reported day 1 through day 42 post-vaccination and a composite end point of moderate or severe injection-site pain/tenderness/soreness or swelling… reported day 1 through day 5 post-vaccination," study authors explained. Of the 698 participants in the study, 459 received the higher-potency dose while 233 received the lower-potency dose.

At 42 days following vaccination, the incidence of systemic clinical AEs, vaccine-related systemic clinical AEs and injection-site AEs other than pain/tenderness/soreness and swelling were comparable between the two treatment groups. "More episodes of moderate or severe injection-site pain/tenderness/soreness or swelling were detected among recipients of the higher-potency zoster vaccine than among recipients of the lower-potency zoster vaccine," investigators observed, "but the incidence rate in the higher-potency vaccine group was below the pre-established clinically meaningful limit."

Complete resolution of moderate to severe injection-site reactions minus swelling was also similar between the two groups at 5.3 days for the higher-potency dose vs. 4.6 days for the lower-potency dose. Swelling resolved within six days with the higher-potency vaccine vs. 5.8 days for the lower-potency vaccine.

"This study supports the acceptable safety and tolerability profile of zoster vaccine at potencies higher than those studied in the SPS," the authors concluded, "and… provides important information on the safety and tolerability of a higher-potency, live attenuated zoster vaccine in a population ≥50 years of age."

Influenza vaccination strongly associated with reduction in all-cause mortality among the elderly

Wang et al. Impact of influenza vaccination on major cause-specific mortality. Vaccine *2007;25(7):1196-203.*

Influenza vaccination is strongly associated with a reduction in not only lung disease-specific mortality but all-cause morbidity and mortality from specific causes including stroke, diabetes and renal disease in an elderly population, according to a study carried out by investigators in Taiwan.

Dr. Chong-Shan Wang, Community Medicine Research Centre and Institute of Public Health, National Yang-Ming University, Taipei, Taiwan, and multicentre colleagues sought to determine whether vaccination against influenza effectively reduced major cause-specific mortality among elderly residents living in southern Taiwan who were ≥65 years of age.

At baseline, 35,637 residents had received the influenza vaccine while 67,061 had not. Over a 10-month observational interval, overall mortality rates for elderly identified as high-risk based on Centers for Disease Control criteria were 8.3% and 2.6% for the low-risk group. Broken down by vaccination status, mortality rates for high-risk elderly individuals were 12.2% for those who were not vaccinated over the 10-month observational interval and 5.4% for those who were. For unvaccinated vs. vaccinated low-risk elderly participants, mortality rates were 3% vs. 1.8% during the same observational interval. For both high- and low-risk elderly individuals, vaccination was significantly associated with a reduction in not only all-cause mortality, but also stroke, pneumonia, chronic obstructive pulmonary disease (COPD), diabetes and renal disease, investigators added. Indeed, vaccine-attributable reductions in mortality for stroke (65%), diabetes (55%) and renal diseases (60%) were even greater than reductions in pneumonia (53%) and COPD (45%). The reasons for this remain unclear but they may be related to the effect that influenza infection may have on systemic inflammation, dehydration and immunosuppression and renal toxicity from antipyretic use. "These results imply that the influence of influenza vaccination on reducing mortality might be much more extensive than stated in previous reports that focused mostly on pneumonia and COPD," the authors observed.

Hepatitis E vaccine protective against infection for at least two years in high-risk population

Shrestha et al. Safety and efficacy of a recombinant hepatitis E vaccine. N Engl J Med *2007;356(9):895-903.*

Infection with hepatitis E (HepE) is clinically indistinguishable from other types of acute viral hepatitis and it is a major public health problem in many developing countries.

According to results from a phase II, randomized trial, a recombinant Hep E vaccine (rHEV) is protective against HepE infection for at least two years in a high-risk population.

Dr. Mrigendra P. Shrestha, Walter Reed-Armed Forces Research Institute of Medical Sciences, Kathmandu, Nepal, and multicentre colleagues assigned 2000 healthy adults who were susceptible to HepE infection to receive either three doses of rHEV or placebo at months 0, 1 and 6. Active surveillance was used to identify acute hepatitis and adverse events, study authors noted, and the primary end point was the development of HepE after three vaccine doses.

A total of 1566 individuals were followed for a median of 804 days. From 14 days after volunteers received the third dose of rHEV to the end of the study, 69 developed HepE, three in the vaccine group and 66 in the placebo controls, producing a vaccine efficacy of 95.5%. From 14 days after the second dose until 14 days after the third dose (a secondary end point of the study), eight participants developed HepE, one in the vaccine group and seven in the placebo group, which translated into an 85.7% efficacy rate. The proportions of participants spontaneously reporting any adverse event were similar in the two study groups, investigators noted, suggesting the vaccine was well tolerated.

"The contribution of rHEV to overall morbidity among the subjects in our trial was substantial and supports the assertion that the burden of HepE is grossly underestimated," the authors commented, adding that in fact, HepE was the most common medically significant illness, including those resulting in hospitalization, disability or death, experienced by placebo controls over the course of the study. Hence, the potential for the rHEV to improve well-being in adults with disease exposure similar to their study population "may be substantial."

Immunogenicity of meningitis vaccine not compromised by room temperature storage for six months

Schöndorf et al. Overcoming the need for a cold chain with conjugated meningococcal Group C vaccine: A controlled, randomized, double-blind study in toddlers on the safety and immunogenicity of Menjugate®, stored at room temperature for 6 months. Vaccine *2007;25(7):1175-82.*

Results of a recent study showed that the immunogenicity of the conjugated meningococcal Group C vaccine is not compromised by storing it at room temperature for six months.

Dr. Ines Schöndorf, Marburg, Germany, together with investigators from the Children's Hospital of Eastern Ontario, Ottawa, compared the safety, reactogenicity and immunogenicity of the vaccine in toddlers after storing the vaccine either at room temperature (25° C) or between 2° and

8° C for six months. As investigators observed, toddlers are the youngest age group recommended to receive a single dose of the vaccine and infants between the ages of 12 and 23 months were studied, as it is this age group that is felt to be the most critical with respect to immunogenicity. "Each subject was observed for 30 minutes after vaccination for immediate post-immunization reactions," investigators reported, and parents kept track of any potential vaccine-related reactions for seven days after the infant had been vaccinated.

A total of 227 toddlers were given the "warm" vaccine while 223 were given the "cold" vaccine and differences in immune responses were measured by rBCA. The per-protocol analysis showed that rBCA titres of at least 1:8 were reached in approximately 88% of infants given the warm vaccine as did virtually identical numbers of infants given the cold vaccine. "At least 70% of subjects in both groups reached an rBCA titre ≥1:128," investigators added, while GMTs were similar between the two groups.

Infants were also stratified by age to ensure that younger infants (12 to <16 months of age) responded as well to the vaccines as did older infants. In this comparison, the GMTs were slightly higher for younger toddlers given the warm vaccine while the reverse was true for older toddlers; nevertheless, further analysis showed no significant relationship between titres achieved and the age of the infants.

As the authors pointed out, the need for a cold chain for vaccine storage increases the cost of immunization both directly and indirectly through wastage, potency loss and the need for repeated immunization. It has been estimated that maintaining the cold chain increases the cost of immunization by about 14% of the total cost. "Thus, the need for temperature-stable vaccines is a priority, especially for developing countries," investigators noted. "The development of more stable vaccines and the exploitation of existing temperature-stable vaccines may reduce the costs of immunization and increase vaccination safety."

Universal hepatitis A immunization program in Israeli educational settings

Belmaker et al. Elimination of hepatitis A infection outbreaks in day care and school settings in southern Israel after introduction of the national universal toddler hepatitis A immunization program. Pediatr Infect Dis J *2007;26(1):36-40.*

A universal hepatitis A (HepA) immunization program introduced into daycare and school settings in southern Israel in 1999 has completely eliminated HepA outbreaks in educational settings, reported investigators. Dr. Illana Belmaker, Ministry of Health (MOH), Southern Regional Office, Beer Sheva, Israel, and multicentre investigators studied the effect of introducing a universal toddler HepA immunization program on subsequent HepA outbreaks in daycare and school settings through to 2005. "The Israeli schedule is a two-dose schedule, the first at 18 months of age and the second at 24 months," investigators noted. Toddlers who were born in January 1998 received their first dose of the vaccine in July 1999 when the program was first initiated, but no catch-up program was used for toddlers born before 1998.

As investigators observed, all HepA cases must be reported to the MOH, which is then responsible for the investigation of each outbreak plus institution of measures to stop the outbreak, including administration of post-exposure prophylaxis. According to their records, over 86% of the birth cohort of 2000 received at least one dose of the HepA vaccine and over 77% received two doses by three years of age.

During the period surveyed, 319 cases of HepA were documented in educational settings, but 306 of them occurred prior to the institution of the universal program in 1999. Another 13 cases were documented in the year 2000 but no cases were reported during the five-year interval from 2001 to 2005. Because no child has been exposed to HepA in a daycare or school setting since 2001, no child has required post-exposure prophylaxis since 2001 vs. an average of 732 children a year who required post-exposure prophylaxis before the universal program was introduced.

As investigators pointed out, the Advisory Committee on Immunization Practices in the US recently recommended routine pre-exposure HepA immunization of all children, with the first dose being given at one year and a second dose six months later. "Our findings support the expectation that the new US immunization recommendations will lead to significant reductions in HepA outbreaks in daycare and school settings in the United States," the authors stated. ❑

UPCOMING EVENTS

National Immunization Awareness Week
April 22-28, 2007

4th International Conference on Vaccines for Enteric Diseases
April 25-27, 2007 / Lisbon, Portugal

10th Annual Conference on Vaccine Research
April 30-May 2, 2007 / Baltimore, Maryland

25th Annual Meeting of the European Society for Pediatric Infectious Diseases
May 2-4, 2007 / Porto, Portugal

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