November / December 2009

VACCINE RESOURCE LINE

A BIMONTHLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

Significant decline in rotavirus activity following introduction of pentavalent vaccine

Centers for Disease Control. Reduction in rotavirus after vaccine introduction—United States, 2000-2009. MMWR Morb Mortal Weekly Rep *2009;58(41)1146-9.*

Prior to the introduction of a vaccine in 2006, rotavirus (RV) caused an estimated 20 to 60 deaths, 55,000 to 70,000 hospitalizations and 205,000 to 272,000 emergency department visits in the US each year.

Sentinel laboratory surveillance carried out by the Centers for Disease Control (CDC) has documented a dramatic decline in RV activity in the US during the first two seasons following the introduction of the pentavalent RV vaccine.

The CDC analyzed data from the National Respiratory and Enteric Viruses Surveillance System from 2007-2008 and from 2008-2009 and compared RV seasons with the pre-vaccine period between 2000-2006. "Results indicated that the 2007-2008 and 2008-2009 seasons were both shorter and later than the median during 2000-2006," the authors reported. For example, compared with the median RV season onset of December from 2000-2006, onset of the 2007-2008 RV season occurred in early March, approximately 11 weeks later. Onset of the 2008-2009 season was in late January, approximately six weeks later than onset during the pre-vaccine season. Furthermore, the duration of the 2007-2008 season was 14 weeks, while the duration of the 2008-2009 season was 17 weeks. The duration of the earlier pre-vaccine RV season was 26 weeks in comparison. Activity also peaked in late April during the 2007-2008 season while it peaked in March during the 2008-2009 season compared with a median peak activity in early March during 2000-2006. The peak percentage of positive RV test results was 17% during the 2007-2008 season and 25% during the 2008-2009 season compared with a median of 43% during 2000-2006.

In their commentary, CDC editors noted that the number of positive test results was 64% lower during the 2007 to 2008 season than in the pre-vaccine period—"more than double the estimated vaccination coverage of 31% for children under 2 years of age." They added, "Although the number of positive test results was somewhat greater and the RV season was longer during 2008 to 2009 compared with 2007 to 2008, RV activity during both seasons was substantially lower than that reported during 2000 to 2006."

The analysis therefore suggests that RV vaccination may provide benefit to both vaccinated and unvaccinated persons by reducing overall transmission through herd immunity.

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Fewer genital warts observed one year after uptake of the quadrivalent HPV vaccine

Fairley et al. Rapid decline in presentations of genital warts after the implementation of a national quadrivalent human papillomavirus vaccination program for young women. Sex Transm Infect *2009 Oct 16 [Epub ahead of print].*
Velicer et al. Prevalence and incidence of HPV genital infection in women. Sex Transm Dis *2009;36(11):696-703.*

A rapid and marked reduction in the incidence of genital warts has been observed only one year after widespread uptake of the quadrivalent human papillomavirus (HPV) vaccine in women up to the age of 26 in Australia.

Dr. Christopher K. Fairley, Melbourne Sexual Health Centre, Victoria, Australia, and multicentre colleagues sought to determine whether the national HPV vaccination program had a measurable impact on clinical presentation of genital warts at a large sexual health service in the year following its implementation. The quadrivalent HPV vaccine was made available in Australia free of charge from April 2007 to girls between the ages of 12 and 13 years in a school-based program, and to a catch-up group of 13- to 18-year-old girls, also in a largely school-based program. From July 2007, the same vaccine was made available free of charge through general practitioners and community immunization clinics for young women up to the age of 26 years.

As the authors reported, of the 36,055 patients who attended the Melbourne Sexual Health Centre for the first time between January 1, 2004 and December 31, 2008, genital warts were diagnosed in 10.6% of the group overall. "Only women under 28 years of age showed strong evidence of a significant difference in the average quarterly change between the two time periods," investigators added, which was a 1.8% increase before the end of 2007 vs. a 25.1%

decrease after the end of 2007. Conversely, there was no evidence of a difference in trends for the quarterly proportions of genital warts diagnosed before and after the end of 2007 for any other subgroup although for heterosexual men in 2008, there was an average quarterly decrease of 5%.

"We saw a marked reduction in clinical presentations for genital warts among women in the target age group for HPV vaccination in the year following the implementation of a national HPV vaccination programme," the authors stated. "The magnitude of the reduction in women less than 28 years indicates a potential for substantial reduction in wart-associated morbidity and costs and has important implications for countries deciding between the bivalent and quadrivalent vaccine."

In a separate study, multicentre colleagues determined the prevalence and incidence of HPV genital infection in a cohort of 3730 women between 24 and 45 years of age. They found that approximately 33% of women in this age group have a prevalent anogenital infection of at least one HPV type and/or are seropositive. Researchers also noted that women in this age group who were seronegative at baseline to the relevant HPV types are at risk for acquiring anogenital HPV infections, as demonstrated by a rate of 10.5% for incidence infections and approximately 5% for persistent infections over a 30-month period.

Probiotic dairy drink increases antibody response to influenza vaccine in healthy elderly

Boge et al. A probiotic fermented dairy drink improves antibody response to influenza vaccination in the elderly in two randomised controlled trials. Vaccine *2009;27(41):5677-84.*

Two separate studies have shown that in individuals over 70 years of age, daily consumption of a commercially available probiotic dairy drink increased specific antibody responses to influenza vaccination and thus may help increase resistance to influenza in the elderly.

Dr. Thierry Boge, Centre Hospitalier de Bourg-en-Bresse, France, and multicentre investigators carried out a pilot study between 2005 and 2006 to determine if regular consumption of a probiotic drink could enhance immune responses to the influenza vaccine in healthy elderly subjects. The product used was a sweetened, flavoured, fermented dairy drink with the probiotic strain *L. casei* combined with ferments commonly used in yogurt.

In the pilot study, 86 healthy elderly individuals were randomized to either the probiotic group or to the control group. "As expected, three weeks after vaccination, antibody levels were significantly higher [two to five times] in both groups for all strains compared to baseline," researchers noted, "but volunteers consuming the probiotic product responded consistently better to the influenza vaccination for the three vaccine strains compared to the control group." At three and five months after receiving the vaccine—a few months after the volunteers stopped consuming the probiotic—antibody titres against the three viral strains had declined to similar levels in both groups.

Based on these pilot findings, investigators carried out a second study involving 222 elderly subjects, 113 of whom were randomized to the same probiotic product and 109 to serve as controls. Antibody levels to all three influenza strains were again significantly higher in both groups following vaccination. However, antibody titres for all three strains were also higher in the probiotic group compared to the control group and remained higher up to nine weeks after vaccination, corresponding to the study product consumption period.

"Results from the two clinical studies... suggest that regular consumption of [a probiotic drink] may aid the immune response to influenza vaccination in the elderly," investigators concluded. "Given that the elderly population eligible to receive such vaccination is large, and taking into consideration the reduced response rates to vaccination observed in this population, consumption of [a probiotic drink] could provide a significant public health benefit by increasing the number of individuals responding to the vaccine."

Opinion leader supports HPV vaccination in males

Shafran SD. The HPV vaccine in men. Can J Diagn *2009; 26(9):89-91.*

In the opinion of infectious disease specialist Dr. Stephen Shafran, Professor of Medicine, University of Alberta, Edmonton, immunizing only females against human papillomavirus (HPV) is inconsistent with the principles of vaccination for common diseases, as no other vaccine licensed in Canada is recommended for just one gender. According to Dr. Shafran, there are also no biological reasons to believe that vaccine efficacy differs by gender.

In his presentation at the University of Alberta's Mountain Man (Men's Health) Third Biennial Conference in June 2009, Dr. Shafran told delegates that studies among male university students indicate that rates of genital HPV infection are at least as high among men as they have been demonstrated to be among women (Partridge et al. *J Infect Dis* 2007;196(8):1128-36). "As in women, increasing numbers of lifetime sexual partners and smoking are risk factors for anogenital HPV infection in men," he observed. A recent study from British Columbia found that the incidence of genital warts was slightly higher among men than among women, he added (Marra et al. *Sex Transm Infect* 2009;85(2):111-5). Many healthcare professionals are also unaware that 32% of all HPV-related cancers occur in men, mainly anal, penile, scrotal and oropharyngeal cancers.

Investigators reported that in a cohort of 10- to 15-year-old males who received the quadrivalent vaccine, anti-HPV titres against the four vaccine types were at least as high as they were in 10- to 15-year-old females as well as females between 16 to 23 years of age who received the same vaccine (Block et al. *Pediatrics* 2006;118(5):2135-45). Another cohort involving over 4000 men between the ages of 16 and 26 years also showed seroconversion rates of 98.9%, 99.2%, 98.8% and 97.4% following three doses of the HPV quadrivalent vaccine to HPV 6, 11, 16 and 18, respectively. In the same cohort of patients, vaccine efficacy against any HPV 6/11/16/18-related external genital lesions was 90.4% and 85.6% against persistent infection.

As Dr. Shafran pointed out, HPV is the most prevalent of all sexually-transmitted infections (STIs), affecting over 50% of men and women. Limiting the number of sexual partners and consistent condom use helps prevent STIs but they are not fully effective against HPV infection because of the "exceedingly high" prevalence of anogenital HPV infection.

"There are two reasons to immunize males against HPV," Dr. Shafran noted. "The first is to prevent morbidity, mortality and healthcare costs related to HPV disease in males... and the second is to protect women from HPV disease by engendering herd immunity. Immunizing only females for HPV infection is a mistake."

Prophylactic antipyretic use reduces antibody responses to vaccine antigens

Prymula et al. Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. Lancet *2009;374(9698):1339-50.*

Prophylactic use of antipyretic drugs at the time of childhood vaccination should not be routinely recommended, multicentre investigators cautioned, as antibody responses to several vaccine antigens were found to be lower in infants receiving prophylactic paracetamol compared with controls.

Dr. Roman Prymula, University of Defence, Hradec Kralove, Czech Republic, and multicentre colleagues assessed the effect of paracetamol on the rate of febrile reactions as well as on geometric mean concentrations (GMCs) to several vaccine antigens given at the time of vaccination and over the next 24 hours. Infants received primary vaccination with a 10-valent pneumococcal non-typeable *Haemophilus influenza* protein D-conjugate vaccine (PHiD-CV) co-administered with the hexavalent diphtheria-tetanus-3-component acellular pertussis-hepatitis B-inactivated poliovirus types 1, 2, and 3-H influenza type b vaccine (DTaP-HBV-IPV/Hib) and oral human rotavirus vaccine, followed by a booster dose of PHiD-CV plus DTaP-HBV-IPV/Hib.

Antipyretic treatment consisted of three doses of paracetamol given via suppositories within the first 24 hours after each vaccine dose, for a total daily dose of between 40 mg/kg and 50 mg/kg. There were 459 infants vaccinated in the primary vaccination study and 414 in the booster study. The mean age of the vaccinated cohort at the time of the first dose was 12.3 weeks while the mean age when infants received the booster dose was 12.7 months. "Fever greater than 39.5° C was uncommon in both groups," investigators reported, occurring in only one vaccine recipient in the prophylactic paracetamol group and three in the non-prophylactic group. After receiving a booster, high febrile rates were seen in only 2% and 1% of each group, respectively. In contrast, the percentage of infants with a temperature of 38° C or higher after one vaccine dose was significantly lower in the prophylactic group after primary vaccination (42%) and after the booster dose (36%) than in infants who received no paracetamol (66%) and for the primary and booster dose (58%).

Investigators also observed an unexpected "substantial reduction" in primary antibody responses to each of the 10 pneumococcal conjugate vaccine serotypes as well as to Hib polysaccharide, diphtheria, tetanus and pertactin antigens. "Before the booster dose, lower antibody GMCs were detected for all vaccine serotypes in the prophylactic paracetamol group than in the non-prophylactic paracetamol group, with fewer children [having] antibody concentrations of 0.20 µg/mL or greater for most vaccine serotypes," they added. Moreover, lower antibody GMCs persisted in the prophylactic group for antitetanus, protein D and all pneumococcal serotypes (except serotype 19F) even after infants had received their booster dose. "Prophylactic paracetamol significantly reduced inflammatory febrile and local pain reactions but had no effect on the occurrence of fever greater than 39.5° C," investigators concluded.

However, the same strategy significantly reduced several vaccine antibody responses independently from its effect on fever. Investigators therefore cautioned that practitioners should weigh the expected benefits of routine childhood vaccination against the risks of using antipyretic drugs when infants are vaccinated.

Pneumococcal vaccine immunogenic into the eighth decade of life

Goldblatt et al. The immunogenicity of 7-valent pneumococcal conjugate vaccine versus 23-valent polysaccharide vaccine in adults aged 50-80 years. Clin Infect Dis *2009;49(9):1318-25.*

Pneumococcal vaccines retain their immunogenicity when given into the eighth decade of life, but a second dose, as assessed by antibody titres alone, has little utility. Dr. David Goldblatt, Institute of Child Health, University College, London, UK, and colleagues and investigators from the Health Protection Agency, Colindale, UK, compared responses to different pneumococcal vaccine formulations in pneumococcal vaccine-naïve adults between the ages of 50 and 80. A total of 599 volunteers were recruited. Vaccinees received either one dose of the 7-valent pneumococcal conjugate vaccine (7vPnC) followed by a dose of the same vaccine or the 23-valent pneumococcal polysaccharide vaccine (PPV) six months later. "Groups were stratified so they contained similar numbers of individuals aged 50 to 59, 60 to 69 and 70 to 80 years," the authors noted. "Concentrations of immunoglobulin G [IgG] specific for the serotypes in 7vPnC were measured before and four to six weeks after each vaccination and one year after enrolment."

Investigators observed that serotype-specific IgG concentrations were typically 10% lower for each 10 years of increasing age and that this effect was similar both prior to the first dose and at month 12. Men were also found to have consistently higher levels of serotype-specific IgG than women. When they then compared geometric mean concentrations (GMCs) of serotype-specific IgG responses after receipt of a single dose of either the 7vPnC or the PPV vaccine four to six weeks after vaccination, they found that the GMCs did differ significantly for four of the seven serotypes. "For serotypes 4, 9V and 23F, 7vPnC was associated with higher GMCs than was PPV," they observed, "while for serotype 19F, IgG concentrations were significantly higher after receipt of PPV."

One year after immunization, the 7vPnC and PPV groups differed in their GMCs for only one serotype, 23F, they added. Regarding responses to a second dose of vaccine (either PPV or 7vPnC) given six months after the initial dose of 7vPnC, the GMCs achieved four to six weeks after the second dose were similar for six of the seven serotypes studied, with the exception of serotype 19F, where GMCs were higher after the PPV dose than the 7vPnC dose. There were also no significant differences between the study groups at any time point in the proportion of subjects with serotype-specific IgG antibody concentrations >0.35 µg/mL or >1.0 µg/mL, putative protective concentrations.

"To our knowledge, this is the first study to formally assess the effect of age [50 to 80 years] on the immune response to 7vPnC

and PPV," investigators commented. "Results show that responses are preserved into the eighth decade and suggest that… there would be little advantage in immunizing adults with PPV at a younger age in an effort to improve primary immunogenicity or induce longer-lasting antibody."

Vaccination strategies for solid-organ transplant candidates

Chow J, Golan Y. Vaccination of solid-organ transplantation candidates. Clin Infect Dis *2009;49(10):1550-6.*

A literature review of vaccination in solid-organ transplantation (SOT) candidates stresses several key strategies, including administration of vaccines early enough in the course of end-organ disease to ensure patients can mount an adequate immune response to the vaccine.

As observed by Drs. Jennifer Chow and Yoav Golan, Division of Geographic Medicine and Infectious Diseases, Tufts Medical Center, Boston, Massachusetts, patients with end-stage renal and liver disease (ESRD and ESLD) have reduced immune responses to vaccines. This means that vaccination should be done as early as possible during the course of the disease, especially since live attenuated vaccines are usually contraindicated in immunosuppressed patients.

Key recommendations from the Advisory Committee of Immunization Practices (ACIP) for SOT candidates include the following:

Hepatitis B vaccine (HBV): The ACIP recommends patients with ESLD or ESRD receive the HBV; because hemodialysis patients as well as patients with ESLD may have a decreased serologic response to vaccination, higher-dose vaccine formulations have been developed for such patients. Patients may also receive the combined HAV and HBV.

Hepatitis A vaccine (HAV): The ACIP recommends patients with chronic viral hepatitis and ESLD receive the HAV or the combined HAV and HBV. HAV serologic responses should be assessed one to three months after completion of the primary HAV series and a single HAV booster dose given to nonresponders.

Pneumococcal vaccine: Pneumococcal vaccination is recommended in patients with chronic organ disease, including ESRD and ESLD, as well as in SOT candidates and recipients. The ACIP also recommends one additional dose be given five years after the first vaccination to patients who receive their initial vaccination before the age of 65 and to the immunosuppressed. The newer heptavalent conjugate vaccine (PCV-7) is not indicated for adult use.

Tetanus, diphtheria and acellular pertussis (TDaP) vaccine: The ACIP currently recommends high-risk patients such as SOT candidates <65 years receive a single dose of TDaP booster which may be given <two years after the last tetanus and diphtheria vaccine.

Human papillomavirus (HPV): The authors recommend the quadrivalent HPV vaccine be given to any female SOT candidate between the ages of nine and 26.

Influenza vaccine: The influenza vaccine has been shown to be safe and to yield adequate antibody responses in SOT recipients. Given that the risks of the trivalent inactivated vaccine are minimal, this vaccine should be given annually to both transplant candidates as well as recipients.

Measles, mumps and rubella (MMR) vaccine: Most adult transplant candidates are already immune to MMR but if they are not by serologic testing, every effort should be made to complete the MMR series before transplantation. Immunity to rubella is particularly important in female transplant candidates who are of childbearing age.

Varicella vaccine: Most adult transplant candidates are already immune to varicella, but because varicella can cause severe disease in immunocompromised patients, vaccination is highly recommended in transplant candidates who are seronegative to varicella. Because the varicella vaccine is a live attenuated vaccine, it is contraindicated in immunocompromised patients.

Herpes zoster (HZ) vaccine: The ACIP recommends patients anticipating immunosuppression receive the HZ vaccine, ideally at least 14 days prior to the initiation of immunosuppression. As with other live vaccines, the HZ vaccine is contraindicated after immunosuppression. □

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