January-March 2011

VACCINE RESOURCE LINE

A QUARTERLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

Prophylactic use of the quadrivalent HPV prevents external genital lesions in boys and men

Giuliano et al. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. N Engl J Med *2011;364(5):401-11, 393-5.*

Prophylactic use of the quadrivalent human papillomavirus (HPV) vaccine is efficacious in preventing external genital lesions (EGLs) associated with HPV 6, 11, 16 or 18 in boys and men between 16 and 26 years of age, according to a large-scale, double-blind, placebo-controlled trial.

Anna Giuliano, PhD, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, and multicentre colleagues randomized 4065 boys and men between 16 and 26 years of age to receive 3 doses of the quadrivalent HPV vaccine or placebo. "A total of 3463 of the subjects were heterosexual," the authors wrote, "and 602 had sex with male partners." Heterosexual subjects were between 16 and 23 years of age and had 1 to 5 female sexual partners during their lifetime while men who had sex with men (MSM) were between 16 and 26 years of age and also reported 1 to 5 male or female partners during their lifetime. As in the female quadrivalent HPV studies, the intent-to-treat (ITT) population may have been seropositive for HPV on enrolment while subjects in the per-protocol population were seronegative on day 1 and PCR-negative from day 1 through month 7 for the relevant vaccine types.

"In the ITT population, 36 EGLs were seen in the vaccine group as compared with 89 in the placebo group, resulting in an observed efficacy of 60.2%," the authors reported. The vaccine was also 65.5% effective against lesions caused by HPV 6, 11, 16 or 18 and reductions were observed in the number of EGLs from both HPV 6 and HPV 11 (59.4% and 76.3% effective, respectively). Reductions in EGLs related to HPV 16 and 18 were non-significant. The efficacy against penile intraepithelial neoplasias (PIN) was not statistically significant in this cohort. No cases of PIN of any grade were observed in the vaccine group vs. 3 cases in placebo controls.

In the per-protocol population, only 6 EGLs were observed in the vaccine group vs. 36 in the placebo group, resulting in an observed efficacy of 83.9%, the authors added. Again, efficacy against EGLs caused by types 6, 11, 16 or 18 was high at 90.4%. Vaccine efficacy differed according to the sexual orientation of subjects, the authors noted: 92.4% effective against EGLs among heterosexual subjects (which was statistically significant) and 79% effective in MSM. The majority of EGLs were condylomata acuminata; against this lesion type, efficacy was 89.4%.

The proportion of subjects who reported 1 or more serious adverse events (AEs) or who discontinued vaccination because of an AE was similar in the 2 groups. "Condylomata acuminata, the most common HPV-related lesion, is associated with substantial physical and psychological morbidity and has a high rate of treatment failure, and treatment of recurrent episodes is costly," investigators wrote. They added that their results would suggest prophylactic vaccination of boys and men with the quadrivalent HPV vaccine might reduce its incidence, as was observed within 3 years after the introduction of the quadrivalent HPV vaccination program in Australia.

Commenting on the findings, Jane Kim, PhD, Harvard School of Public Health, Boston, Massachusetts, noted that the report "undoubtedly gives us cause to celebrate the extraordinary potential for HPV vaccination to improve health in both women and men." She also indicated that newer data have shown that the quadrivalent vaccine is effective in preventing anal intraepithelial neoplasia, a precursor to anal cancer in men, particularly in MSM. On the basis of this new evidence, the U.S. Food and Drug Administration recently approved the expanded use of the quadrivalent vaccine to include the prevention of anal lesions and cancer in both sexes.

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A notable reduction in AMI rate during the first 60 days after influenza vaccination

Gwini SM, Coupland CA, Siriwardena AN. The effect of influenza vaccination on risk of acute myocardial infarction: Self-controlled case-series study. Vaccine *2011;29(6):1145-9.*

Further evidence supports findings from a self-controlled case-series study, where a notable reduction in the rate of acute myocardial infarction (AMI) among older adults was reported during the first 60 days after they were vaccinated against influenza.

Researcher Stella May Gwini, MSc, Monash University, Melbourne, Australia, and multicentre colleagues extracted data from the General Practice Research Database (GPRD) using cases of first-time AMIs occurring between January 9, 2002, and May 31, 2007. "The GPRD is a large, well-validated computerized data with anonymized representative patient data... including AMI and deaths, covering 5% of the UK population," the authors explained. A case was defined as any patient at least 40 years of age when diagnosed with a first AMI within the observation period. A total of 13,978 first cases of AMI were identified during this time.

"Of these, 2887 did not receive any influenza vaccination during the observation period, 2875 had AMI diagnosis dates before their first influenza vaccination during the study period and 36 had AMI diagnosis dates identical to influenza vaccination dates," the authors stated. This left 8180 cases of AMI for the final analysis.

In total, cases received 30,507 influenza vaccinations during the study period; 87.7% of these were classified as "early vaccinations" from September 1 to November 15. "There was a significant reduction in the rate of AMI for the 1-14 days prevaccination interval and in the 1-14 days, 15-28 days and 29-59 days' post-vaccination intervals compared with the baseline period," they reported. Seasonally adjusted incidence rate ratios in the post-vaccination periods showed reduction in AMI rates ranging from 32% in the 1-14 days after vaccination to 18% in the 29-59 days' post-vaccination. "Reductions in AMI incidence were more pronounced for early seasonal vaccinations before mid-November," they noted, "[but] we found no significant difference between patterns of risk in males and females."

As investigators explained, they wanted to explore the association between AMI and influenza vaccination using this self-controlled case-series method, which allows a comparison of the incidence of first AMI in different time periods following vaccination. Cases act as their own control in periods when they are not exposed, they explained, and this therefore accounts for unmeasured confounding variables, provided they are constant over time within individuals.

"This study... lends support to previous studies showing a beneficial effect of influenza vaccination," the authors concluded. "Our findings strengthen current recommendations for annual influenza vaccination of risk groups and may help improve suboptimal vaccination rates, particularly in those aged under 65 years in the UK."

Early introducers of rotavirus vaccines show rapid and substantial reductions in severe childhood diarrhea

Patel et al. Real-world impact of rotavirus vaccination Pediatr Infect Dis J *2011;30(1 Suppl): S1-S5.*

The effect that the 2 currently available rotavirus (RV) vaccines have had on the burden of severe childhood diarrhea in countries in which the vaccines were introduced early has been rapid, substantial and easily measured, according to an editorial overview in a supplement devoted to RV vaccination in *The Pediatric Infectious Disease Journal.*

As Dr. Manish Patel, Centers for Disease Control and Prevention, Atlanta, Georgia, and colleagues noted, since the RV vaccines were first introduced into national immunization programs in 2006, "dramatic" reductions in severe and fatal childhood diarrhea have been observed in a variety of low-middle, middle and high-income countries.

In Mexico, for example, where the vaccines were first introduced as part of regular childhood immunization in May 2007, a 40% reduction in hospitalizations for childhood diarrhea was observed during the 2009 RV season. Investigators also reported a large reduction in laboratory-confirmed RV disease in El Salvador that was sustained for 2 years after RV vaccine introduction in the country. In Australia, where the RV vaccine was introduced in July 2007, there was an 89% to 94% reduction in childhood RV disease in the 2 years following its introduction, while in the US, childhood RV disease has also been dramatically reduced.

Furthermore, there have been substantial indirect benefits following introduction of RV vaccination, Dr. Patel continued.

Post-vaccination data during the early years after its introduction indicate that there have been large reductions in RV disease among children who were too old to be vaccinated. "All in all, the countries represented in this... supplement have a combined birth cohort of ~7 million infants, most of whom are now receiving RV vaccination," Dr. Patel wrote. "The observed reductions in these early introducer countries suggest that the fraction of diarrhea caused by RV is greater than that estimated on the basis of prevaccine surveillance. The time to introduce these lifesaving interventions is now."

Decline in varicella-related hospitalizations in the US continues in the 1-dose varicella vaccination era

Lopez et al. Varicella-related hospitalizations in the United States, 2000-2006: The 1-dose varicella vaccination era. Pediatrics *2011;127(2):238-45.*

Further documentation of a continued decline in varicella-related hospitalizations during the 1-dose varicella vaccination era have again been demonstrated using data from two large databases that have been tracking hospitalization trends in the US over the last number of decades.

Adriana Lopez, MHS, Centers for Disease Control and Prevention, Atlanta, Georgia, and colleagues from there and from the National Center for Immunization and Respiratory Diseases, analyzed 1988-2006 data from the National Hospital Discharge Survey (NHDS) as well as 1998-2006 data from the Nationwide Inpatient Sample (NIS) to calculate numbers and rates of varicella-related hospitalizations after implementation of the varicella vaccination program. "We defined the prevaccination era as 1988-1995, the period before licensure and widespread use of the varicella vaccine," the authors noted, "while the 1-dose vaccination era was defined as the years 2000-2006, a period when 1-dose national varicella coverage was >65% and before implementation of the universal 2-dose vaccination recommendation."

Based on NHDS data, the overall varicella-related hospitalization rate was 0.12/10,000 population in the 1-dose era vs. 0.42/10,000 population in the pre-vaccination era ($P<0.01$). Again on the basis of NHDS data, "The estimated average annual varicella-related hospitalization rates... decreased by >70% in all age groups younger than 20 and by 65% in the 20-and-older age group during the 1-dose vaccination era compared with the prevaccination era ($P<0.001$)," the authors added. Hospitalization rates remained highest for children between the ages of 0 and

4 years but they were still 72% lower during the 1-dose era than during the prevaccination era ($P<0.001$). The mean length of varicella-related hospitalization during the 1-dose era was 4.6 days, which corresponded to 16,149 days of hospitalization annually. This compared with a mean of 5.4 days during the prevaccination era, which corresponded to 56,975 days of hospitalization annually.

On the basis of NIS data, the overall varicella-related hospitalization rate during the 1-dose era was 0.09/10,000 population and 17/10,000 varicella cases—lower than NHDS rates. Hospitalization rates were again highest among the 0- to 4-year-old group according to NIS data but were still 70.1% lower when comparing 2000 with 2006 ($P<0.001$).

"Assuming that declines in varicella-related hospitalizations are due, in large part, to the routine childhood varicella vaccination program, these data suggest that varicella vaccination prevented ~50,000 varicella-related hospitalizations in the United States from 2000 to 2006," the authors stated. They suggested that given the current recommendation for a second dose of varicella vaccine at 4 to 6 years, "it is expected that the implementation of this recommendation will lead to additional declines in varicella incidence and hospitalization rates."

Herpes zoster vaccine highly effective in community-dwelling seniors

Tseng et al. Herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease. JAMA *2011;305(2):160-6.*

The herpes zoster (HZ) vaccine has been shown to dramatically reduce the incidence of HZ, especially ophthalmic zoster and the need for hospitalization for an acute episode, among community-dwelling immunocompetent seniors compared with unvaccinated controls. The reduction in the incidence of HZ disease following receipt of a single dose of the HZ vaccine was also independent of age, race or presence of chronic diseases, according to findings from a large retrospective study carried out in the US.

Hung Fu Tseng, PhD, Southern California Kaiser Permanente, Pasadena, and multicentre colleagues carried out a retrospective cohort study from January 1, 2007, through to December 31, 2009, in which individuals 60 years of age and older enrolled in the Kaiser Permanente Southern California health plan took part. A total of 75,761 members of the HMO received the HZ vaccine and 227,283 age-matched controls did not. The incidence of HZ was compared over an average follow-up of 1.56 years for the unvaccinated cohort and 1.72 years for the vaccinated cohort.

As investigators reported, they identified a total of 5434 cases of HZ in the overall cohort, at an incidence rate of 13.0/1000 person-years among the unvaccinated cohort vs. 6.4/1000 person-years among vaccinees in univariate analysis. In the fully adjusted analysis, the vaccine reduced the incidence of HZ by 55% (HR 0.45), as well as the risk of ophthalmic HZ by 63% (HR 0.37) and hospitalizations coded as HZ by 65% (HR 0.35). As expected, among the unvaccinated cohort, HZ increased with age ≥80; it was lower in both males and African Americans and varied by chronic disease, occurring more often in individuals with lung disease.

As the authors pointed out, their data complement results of the original Shingles Prevention Study (SPS) which was carried out in a select study population treated under idealized conditions.

Furthermore, "the efficacy of the HZ vaccine at preventing ophthalmic HZ was not assessed in the SPS," the authors pointed out, "and our finding that vaccine recipients had a reduced risk of these episodes was therefore particularly important."

So far, uptake of the vaccine has been poor due to both weaknesses in adult vaccine infrastructure as well as serious barriers to its use among clinicians and patients, as the authors remarked. "Solutions to these challenges need to be found so that individuals seeking to receive HZ vaccine will be able to reduce their risk of experiencing this serious condition," the authors stated. "This vaccine has the potential to annually prevent tens of thousands of cases of HZ and postherpetic neuralgia nationally."

Timely intervention with MMR vaccine prevents measles in exposed susceptible children

Barrabeig et al. Effectiveness of measles vaccination for control of exposed children. Pediatr Infect Dis J *Epub September 14, 2010.*

One dose of the measles-mumps-rubella (MMR) vaccine administered within 72 hours after rash onset in an index case is highly effective in preventing measles in susceptible contacts, according to a Spanish study.

Dr. Irene Barrabeig, Epidemiological Surveillance Unit of Costa Ponent, Barcelona, Spain, and multicentre colleagues evaluated the effectiveness of the measles vaccine for post-exposure prophylaxis (PEP) in education centres. "A total of 166 children (median age 16.5 months) who shared a classroom with 10 confirmed cases during the infectious period of the cases were studied," they noted. The 10 index cases had not been vaccinated against MMR; most were between the ages of 6 and 14 months although 2 were between 15 months and 4 years of age.

The median infectious period in the classroom was 2 days. In all, 90 (54%) of the children had received 1 dose of the MMR and 1 (1%) had received 2 doses; 75 (45%) had not been vaccinated, nor had they contracted measles. "Of the 75 candidates for the intervention, 25 contracted measles, of which 12 had received the vaccine as PEP," investigators reported. The median age of this cohort was 12.2 months. Out of the 75 children who were exposed to an index case, 54 were vaccinated or 72% overall, at a median intervention time of 5 days. The secondary attack rate among vaccinated children was 22% compared with 62% in unvaccinated children; among children who received the vaccine within ≤72 hours, the secondary attack rate was 5.9%, for a vaccine efficacy of 90.5% compared with unvaccinated children ($P<0.001$).

In contrast, administration of the vaccine was not effective (54%) in children who received the vaccine within 4 to 5 days of exposure. As investigators acknowledged, vaccination of susceptible contacts in centres cannot be carried out on the same day the index case is diagnosed and in their own study, vaccination on the day after clinical suspicion was only achieved in 12 children. Indeed, only 17 out of the 54 susceptible contacts were vaccinated within 72 hours.

"Given the difficulty of carrying out vaccination within this time, achieving and maintaining high routine vaccination coverage from 12 months onwards is the essential strategy to avoid measles outbreaks," they concluded.

Routine vaccination may protect children against certain cancers

Pagaoa et al. Associations between vaccination and childhood cancers in Texas regions. J Pediatr *Epub January 11, 2011.*

Routine childhood vaccination may protect children against the development of certain cancers, according to a study of childhood cancers and vaccination coverage in the state of Texas.

Melissa Pagaoa, MPH, University of Texas School of Public Health, Houston, and multicentre colleagues carried out a case-control study using multi-level data to examine the association between vaccination rates in Texas and certain childhood cancers, acute lymphoblastic leukemia (ALL) in particular, medulloblastoma and non-Hodgkin lymphoma (NHL). Investigators used the Texas Cancer Registry to identify 2800 cases in Texas-born children between 2 and 17 years of age who had been diagnosed with cancer between 1995 and 2006. "For the final analyses, a total of 2800 cases and 11,200 control subjects were available to measure the association between vaccination coverage rates and childhood cancer," the authors stated. Among the children who had been diagnosed with cancer, 32% had been diagnosed with ALL, 4.1% with medulloblastoma and another 4.1% with NHL.

Analyses revealed that children born in counties with higher hepatitis B vaccine coverage rates had a 19% lower risk of all cancers combined (OR 0.81) and a 37% lower risk of developing ALL (OR 0.63). A decreased risk for ALL was similarly seen at the county level with the highest rates of inactivated poliovirus vaccine coverage and the 4-3-1-3-3 vaccination series at 33% and 38%, respectively. Children born in public health regions with higher coverage levels of the *Haemophilus influenzae* type b-conjugate vaccine also had a 42% lower risk of developing ALL (OR 0.58), investigators added. As the authors pointed out, because they used a large pool of population-based control subjects, the distribution of potential risk factors between cases and controls was similar, thereby reducing the possibility that significant results were due to confounding factors.

"The biologic mechanism behind the effect of vaccinations on childhood cancer remains to be determined," investigators noted, "[but] our results corroborate findings from previous studies that point to a reduced risk from common vaccines against the development of ALL. Immunization programs may not only reduce the number of infectious diseases in childhood but also contribute to some immunologic defense against the development of certain cancers."

Revised ACIP adult immunization schedule for 2011

Advisory Committee on Immunization Practices. Recommended adult immunization schedule: United States, 2011. Ann Intern Med *2011;154(3):168-73.*

The adult immunization schedule in the US for 2011 has been slightly revised by the Advisory Committee on Immunization Practices (ACIP) to reflect current recommendations for licensed vaccines.

The 2011 adult immunization schedule is available at www.cdc.gov/vaccines/recs/schedules/adult-schedule.htm. □

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