Autumn-Winter 2011

VACCINE RESOURCE LINE

A QUARTERLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

Decreased incidence of high-grade cervical abnormalities 3 years after Australian HPV program launch

Brotherton et al. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. Lancet *2011;377:2085-92.*

Anhang Price et al. Knowledge and intention to participate in cervical cancer screening after the human papillomavirus vaccine. Vaccine *2011;29:4238-43.*

Australia is reporting a significant decrease in the incidence of high-grade cervical abnormalities (HGAs) in females under the age of 18 only 3 years after the start of the national quadrivalent human papillomavirus (HPV) vaccine program in the country.

Dr. Julia Brotherton, Victorian Cytology Service, East Melbourne, Australia, and colleagues compared the incidence of histopathologically defined HGA including cervical intraepithelial neoplasia (CIN) 2+, adenocarcinoma in situ (AIS) and low-grade cytological abnormalities in 5 age groups before and after the introduction of the vaccination program in April 2007. "After the introduction of the vaccination programme, we recorded a decrease in the incidence of HGAs by 0.38%... in girls younger than 18 years," they reported. This decrease was progressive, they added, and began shortly after the program was launched.

Specifically, researchers observed a reduction in HGA from 0.85% in 2006—the year before the vaccination program started—to 0.22% in 2009 (P=0.003). In females between the ages of 18 and 20, a decrease in the incidence of HGA seems to have begun about 1.5 years after the introduction of the vaccine, they noted. Early data from sexual health clinics in Australia have already shown that the incidence of genital warts in Victoria began to decrease in the first year of the vaccination program. Australia was the first country to institute an extensive, funded, national HPV vaccination program with the quadrivalent vaccine within the context of an already intensive and successful national cervical screening program.

Much discussion has surrounded the possibility that women, unduly reassured about the cancer prevention benefits of HPV vaccination, may not participate in cervical cancer screening. However, out of 1586 females respondents between the ages of 18 and 74 involved in the 2008 Health Information National Trends Survey (HINTS) in the US, more than 95% knew that HPV-vaccinated women should continue to receive Pap tests. Among females who had already had the Pap test, recipients of the HPV vaccine were actually more likely than those who had not been vaccinated to indicate they planned to receive a Pap test within 3 years.

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PCV7 vaccine given at birth safe, immunogenic in vulnerable young infants

Scott et al. Pneumococcal conjugate vaccine given shortly after birth stimulates effective antibody concentrations and primes immunological memory for sustained infant protection. Clin Infect Dis *2011;53(7):663-70.*

The first dose of the 7-valent pneumococcal conjugate vaccine (PCV7) given within 72 hours of birth is safe and immunogenic and offers an alternative strategy to control invasive pneumococcal disease (IPD) in vulnerable young infants.

Dr. Anthony Scott, Wellcome Trust Research Programme, Kilifi, Kenya, and multicentre colleagues randomized a total of 300 infants to either an Expanded Programme on Immunization (EPI) vaccine schedule or to a newborn schedule. The EPI group received the PCV7 vaccine at 6, 10 and 14 weeks of age and the newborn group received the same vaccine at 0, 10 and 14 weeks of age. "At 36 weeks of age, each infant received a booster of either the 7-valent PCV or a 20% fractional dose 0.1 mL of the 23-valent PPV concomitantly with the measles vaccine," the authors reported.

Thirty minutes after receiving their first dose of the PCV7 vaccine, 5.3% of infants in the EPI group and 6.7% of the newborn group developed a temperature of 37.5° C or more. Between birth and 9 months of age, 38 serious illnesses requiring hospitalization were documented in the EPI group vs. 32 in the newborn group—"none of which was related to vaccination," as investigators pointed out.

At 18 weeks of age, the proportion of infants who had attained the protective threshold of 0.35 µg/mL was ≥87% for antibodies to all vaccine serotypes with no significant differences by vaccine group. Geometric mean concentrations (GMCs) of anticapsular IgG were higher in the EPI group for 4 of the 7 serotypes at 18 weeks; by 36 weeks, "these differences had disappeared except for serotype 4, in which the GMC remained greater in the EPI group," the authors wrote. Again at 36 weeks, the proportion of infants with anticapsular IgG above the protective threshold was significantly higher in the EPI group for serotype 4 only.

"To our knowledge, this is the first study to report the safety and humoral immunogenicity of PCV at birth," investigators

stated, "[and we found that] the newborn schedule of 7-valent PCV was immunogenic at 18 weeks and induced immunological memory, as indicated by brisk booster responses at 36 weeks, with no evidence of immunological tolerance."

As the authors noted, IPD is uncommon in neonates in the industrialized world but in Gambia, for example, the burden of disease in infants under 60 days of age is notable. In Kenya, the incidence of IPD is highest in young infants.

Adults not exposed to varicella not at increased risk of herpes zoster

Gaillat et al. Does monastic life predispose to the risk of Saint Anthony's fire (herpes zoster)? Clin Infect Dis *2011;53(5):405-10.*

Monastic adults who are not exposed to the varicella zoster virus (VZV) are not at increased risk to develop herpes zoster later in life, a finding that challenges current assumptions that widespread varicella vaccination in childhood could potentially increase the risk of herpes zoster in adulthood.

Dr. Jacques Gaillat, Annecy General Hospital, Pringy, France, and multicentre colleagues compared the frequency and age of onset of herpes zoster among members of contemplative monastic orders (CMOs) of the Roman Catholic Church to that in the general French population (GP). "The primary objective was to evaluate the frequency of zoster in a population not exposed to children (CMO members) in comparison with that in the GP," the authors explained. A total of 1533 subjects from the GP were compared to 920 CMO members.

In the primary analysis, the reported frequency of herpes zoster among CMO members was 16.2% compared to 15.1% in the GP. Mean age of onset was 54.8 years in CMO members vs 48.6 years in the GP, investigators added.

"To our knowledge, this is the first study designed to evaluate an association between an increased risk of zoster in adults and the absence of contact with children with varicella," investigators stated. As they discussed, young healthy adults rarely develop herpes zoster, in theory because adults who come in contact with chickenpox reinforce their anti-VZV, cell-mediated immunity from repeated exposure, thereby reducing their risk of herpes zoster—a process referred to as exogenous boosting.

"All epidemiological models designed to predict the consequences of routine childhood [varicella] vaccination program incorporate exogenous boosting," they noted, "and this means that all consider repeated contacts with varicella reduce the risk of zoster to be equivalent to the unproven assumption that the absence of contact with varicella causes an increased risk of zoster." In other words, all of the models predicting high uptake rates of varicella vaccine coverage in childhood would prompt the disappearance of chickenpox from childhood but would increase the number of cases of zoster in young adults. However, as shown by this multicentre, observational, epidemiological study, adults who are not exposed to the VZV are not at increased risk of herpes zoster compared with the GP suggesting that age-related risk of herpes zoster is due to immunologic senescence.

The Shingles Prevention Study showed that the herpes zoster vaccine led to an approximately twofold reduction in the incidence of herpes zoster vs. placebo in adults 60 years of age and older and an approximately threefold reduction in the incidence of post-herpetic neuralgia.

US rotavirus vaccination program dramatically reduces paediatric hospitalization for rotavirus infection

Payne et al. Direct and indirect effects of rotavirus vaccination upon childhood hospitalization in 3 US counties, 2006-2009. Clin Infect Dis *2011;53:245-53.*

Macartney et al. Decline in rotavirus hospitalisations following introduction of Australia's national rotavirus immunisation programme. J Paediatr Child Health *2011;47:266-70.*

Introduction of the rotavirus vaccination program in the US has led to dramatic reductions in hospitalization rates for rotavirus infection in young children, according to results from a sentinel hospital surveillance study. In fact, the observed reductions seen in 2008 far exceed what was expected on the basis of vaccine coverage and likely resulted from direct protection conferred by younger, vaccinated children within the household and the community.

Dr. Daniel Payne, Centers for Disease Control and Prevention, Atlanta, Georgia, and multicentre colleagues conducted an active, population-based surveillance for rotavirus gastroenteritis hospitalizations in 3 US counties. In February 2006, the US Advisory Committee on Immunization Practices (ACIP) recommended universal vaccination of US infants using the then available pentavalent vaccine, given orally to infants at 2, 4 and 6 months of age. A second rotavirus vaccine (monovalent) was recommended by the ACIP in April 2008. (Over 95% of the children in this surveillance study received the pentavalent vaccine.)

A total of 837 children <3 years old who were hospitalized with acute gastroenteritis (AGE) were enrolled from January through June for 4 consecutive rotavirus seasons (2006-2009) at the 3 New Vaccine Surveillance Network (NVSN) surveillance sites. A total of 725 stool specimens were collected; of these, 36% tested positive for rotavirus.

By study year, 51%, 52%, 6% and 26% tested positive for rotavirus during 2006, 2007, 2008, and 2009, respectively. Reflected by hospitalization rates, in 2006, there were 22.5 hospitalizations per 10,000 children <3 years old, 21.6 per 10,000 children in 2007 and 2.4 per 10,000 children in 2008—a 89% decrease in hospitalization due to rotavirus infection compared with the 2006 reference year, as the authors indicated. In 2009, the rotavirus infection hospitalization rate was 10.1 per 10,000 children, greater than the rate in 2008 but still 55% lower than the baseline rate in 2006. Vaccination coverage also increased with each surveillance year, from 0% in 2006 to 10% in 2007, 42% in 2008 and 67% in 2009.

As investigators pointed out, reductions in hospitalization rates for AGE occurred even among children who were too old to have been immunized. "This observation was likely caused by disrupted rotavirus transmission among household and community contacts following the large increase in vaccination coverage in 2008," they reported, a phenomenon that was not studied in the clinical trials of either vaccine.

In Australia, Kristine Macartney, National Centre for Immunization Research and Surveillance, New South Wales, and multicentre colleagues also observed that hospitalizations for rotavirus gastroenteritis declined by 75% in the 2 full rotavirus seasons—2008 and 2009—after introduction of the vaccine compared with mean annual hospitalization rates from 2001 to 2006. "The greatest decline was seen in those <12 months of age—93%—but the reduction occurred consistently across all age groups, even in children not eligible for immunization," they

stated, suggesting a herd immunity effect. Australian researchers also reported a "substantial decline" in nosocomial rotavirus gastroenteritis from 2007 to 2009, again suggesting a reduction in virus transmission not only in the community but in the hospital setting as well.

Non-typeable *Haemophilus influenzae* most common pathogen in Australian children with recurrent AOM

Wiertsema et al. Predominance of nontypeable Haemophilus influenzae *in children with otitis media following introduction of a 3 + 1 pneumococcal conjugate vaccine schedule.* Vaccine *2011;29:5163-70.*

The predominant pathogen colonizing the nasopharynx and middle ear of non-Aboriginal Australian children with recurrent acute otitis media (rAOM) is non-typeable *H. influenzae* (NTHi), according to an Australian study.

Two to 4 years after the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) into the Australian National Immunisation Program, NTHi and *Streptococcus pneumoniae* carriages rates were significantly higher in children with a history of rAOM at 56% and 41%, respectively, compared with healthy controls at 19% and 26%, respectively. In contrast, "carriage of PCV7 pneumococcal serotypes was rare," as observed by the authors under lead author Dr. Selma Wiertsema, University of Western Australia, Perth. Serotype 19A accounted for 39% of isolates.

Children under the age of 36 months either had a history of rAOM requiring ventilation tube insertion (n=186) or had no history of rAOM (n=81). Of those with a history of rAOM, 43 did not have middle ear effusion at the time of study enrolment, 97 had bilateral effusion and 46 had unilateral effusion; all children were asymptomatic at the time of sample collection. Virtually all of the children (98%) had also received all 3 doses of the PCV7 vaccine at 2, 4 and 6 months of age, with no booster dose.

"In children with rAOM, 79% of the nasopharyngeal swabs were culture-positive for at least one major otopathogens (*S. pneumoniae*, NTHi and *Moraxella catarrhalis*) compared with 53% of healthy children ($P<0.0001$)," the authors reported. Interestingly, among the 143 children with rAOM from which middle ear effusion was collected, 73% were culture-negative; again, NTHi was the most common pathogen which was present in middle ear effusions.

Frailty in elderly associated with decreased antibody response to the trivalent inactivated influenza vaccine

Yao et al. Frailty is associated with impairment of vaccine-induced antibody response and increase in post-vaccination influenza infection in community-dwelling older adults. Vaccine *2011;29:5015-21.*

Frailty is associated with a decreased antibody response to the trivalent inactivated vaccine (TIV) and increased rates of post-vaccination influenza-like illness (ILI) and influenza infection in community-dwelling older adults, according to a joint study carried out in the US and Taiwan.

Dr. Xu Yao, Johns Hopkins University School of Medicine, Baltimore, Maryland, and multicentre colleagues evaluated TIV-induced strain-specific hemagglutination inhibition (HI) antibody titres as well as post-vaccination rates of ILI and laboratory-confirmed influenza infections in frail and nonfrail older adults. A final sample size of 71 subjects, mean age 84.5 years, was enrolled.

Using a validated set of criteria to identify seniors who are frail and vulnerable to adverse health outcomes, investigators identified 17 of them as frail, 32 as pre-frail and 22 non-frail. The population as a whole "had significantly higher post-immunization HI titres compared to pre-immunization HI titres to H1N1, H3N2 and B strains," the authors noted. Nonfrail subjects had significantly higher post-immunization HI titres to all 3 strains as did pre-frail participants to both H1N1 and H3N2 but not HI titres to B strain. "In contrast, there was no statistically significant difference between post-immunization and pre-immunization HI titres to any of the [3] vaccine strains among frail participants," the authors observed.

Furthermore, post-immunization HI titres to all 3 vaccine strains showed a significant stepwise decrease from the nonfrail to the pre-frail to the frail, adjusted for age. Rates of seroprotection (HI titre ≥1:40) were high to all 3 strains and they did not differ among nonfrail, prefrail and frail study groups, investigators indicated.

Conversely, rates of seroconversion, defined as a fourfold or higher post-over pre-immunization HI titre rise, were low to all 3 vaccine strains in all 3 study groups. The authors also noted that 26.8% of participants developed ILI during the post-vaccination season while 15.5% of them had confirmed influenza infection. Once again, rates of ILI and confirmed influenza infection showed a significant stepwise increase from the nonfrail and pre-frail to frail participants at 9%, 25% and 53%, respectively, for ILI and 5%, 16% and 29%, respectively, for influenza infection.

"Findings from this study provide initial evidence suggesting that assessing frailty status in the elderly may identify those who are less likely to respond to TIV immunization and [who] might be at higher risk for seasonal influenza and its complications," investigators concluded.

Improved immunogenicity, no excess reactogenicity in very young children given 2 influenza vaccines

Della Cioppa et al. Trivalent and quadrivalent MF59-adjuvanted influenza vaccine in young children: A dose- and schedule-finding study. Vaccine *2011. In press (doi:10.1016/j.vaccine.2011.08.111).*

Significantly improved immunogenicity with no excess reactogenicity has been observed in a dose- and schedule-finding study in which both a trivalent (TIV) and a quadrivalent (QIV) MF59-adjuvanted influenza vaccine was given to children between 6 and <36 months of age.

Clinical scientist Dr. Giovanni Della Cioppa, Siena, Italy, and multicentre colleagues evaluated the safety and immunogenicity of different vaccine formulations with different doses of MF59 adjuvant with or without a second B strain added to either high or low doses of a purified subunit influenza vaccine. A total of 410 children participated in this multicentre, randomized trial.

As investigators reported, the study confirmed that the immunogenicity of non-adjuvanted influenza vaccines is suboptimal in young children. Findings also confirmed that the addition of the MF59 adjuvant—an oil-in-water emulsion containing naturally occurring squalene—promotes

hemagglutination inhibition (HI) antibody responses to levels associated with protection in adults not achieved by non-adjuvanted vaccines and with no impact on reactogenicity and safety in these young children. The study also showed that a second influenza B strain, when combined with the traditional TIV vaccine, is immunogenic and does not affect the immunogenicity of the other 3 influenza strains.

Lastly, investigators observed that the MF59-adjuvanted TIV and QIV vaccines already show a meaningful immune response to influenza A strains after one dose. "This may be beneficial in real-life clinical practice where a second dose is often missed," they noted.

Since the early 1980s, 2 distinct lineages of B influenza strains have often co-circulated in humans and there is no cross-protection between these lineages.

HPV vaccine uptake among US adolescent males nonexistent one year after national recommendations

Reiter et al. HPV vaccine and adolescent males. Vaccine *2011; 29:5595-602.*

Uptake of the quadrivalent human papillomavirus (HPV) vaccine one year after national recommendations were first issued for its use in males has been nearly nonexistent, according to a large survey of parents and their sons by American investigators.

Dr. Paul Reiter, School of Global Health, and colleagues from the Lineberger Comprehensive Cancer Center, Chapel Hill, North Carolina, invited 1195 parents by e-mail to participate in the HPV Immunization in Sons (HIS) survey, 547 of whom completed the survey as did 421 of their sons. "Only 2% (12/547) of sons had received any doses of the HPV vaccine, of which only 2 (<1%) had received all 3 doses," investigators reported. Six parents with vaccinated sons indicated the main reason their son had been vaccinated was because a physician recommended the vaccine.

Among parents whose sons had not been vaccinated, "80% [were] unaware that the HPV vaccine can be given to males," the authors added. Similar to parents, some 90% of the sons were unaware that they were eligible for the HPV vaccine and most had never heard of HPV before completing the survey. Sons also did not feel it was very likely that they would get HPV-related disease. In general, parents whose sons had not been vaccinated were not concerned about their sons getting HPV-related disease and very few parents reported that their sons' doctors had recommended their sons be vaccinated.

Were the vaccine to be free of charge, parents indicated that they were moderately willing to have their sons vaccinated. Sons also indicated they were moderately willing to get the HPV vaccine, and they were more willing to get vaccinated if their sisters had received the HPV vaccine.

"To our knowledge, this represents the first estimate of HPV vaccine uptake among adolescent males in the US," investigators stated, "and the observed uptake rate is noticeably lower than that among adolescent females about a year after HPV vaccine licensure occurred for them (10% to 30% in 2007)."

Getting physicians to discuss the HPV vaccine was considered vital by investigators, as health care providers will play an "increasingly important role" in vaccine acceptability and uptake as time since vaccine licensure for males passes. The authors also suggested that targeting health care providers might help increase HPV vaccine acceptability and uptake among males. □

UPCOMING EVENTS

49th Annual Meeting of the Infectious Diseases Society of America (IDSA)
October 20-23, 2011 / Boston, MA
http://www.idsa2011.org/

12th IUSTI World Congress of Sexually Transmitted Infections & AIDS
November 2-5, 2011 / New Delhi, India
http://delhi.iusti2011.org/home

2011 Annual Meeting of the American College of Allergy, Asthma & Immunology
November 3-8, 2011 / Boston, MA
http://www.acaai.org/about/Pages/AnnualMeeting.aspx

7th World Congress of the World Society for Pediatric Infectious Diseases
November 16-19, 2011 / Melbourne, Australia
http://www2.kenes.com/wspid/pages/home.aspx

International Conference and Exhibition on Vaccines & Vaccination
November 22-24, 2011 / Philadelphia, PA
http://omicsonline.org/vaccines2011/

World Influenza Congress Europe 2011
December 6-8, 2011 / Vienna, Austria
http://www.terrapinn.com/2011/flu/index.stm

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