

# VACCINE

## RESOURCE LINE

A BIMONTHLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

### Vaccination against high-risk HPV types to reduce lesions and cervical cancer

Moore et al. *Prevalence and type distribution of human papillomavirus in 5,000 British Columbia women—implications for vaccination*. *Cancer Causes Control* 2009 May 29.

An estimate of the prevalence of human papillomavirus (HPV) in women participating in routine cytology screening in British Columbia indicates that vaccination against high-risk oncogenic HPV types would prevent the development of at least one-third of low-grade intraepithelial lesions (LGIL) and more than half of high-grade IL (HGIL) and an even larger proportion of cervical cancer.

Dr. Richard Moore, BC Cancer Agency, Vancouver, and multicentre colleagues identified HPV prevalence and type distribution in 8660 women who participated in a population-based cervical cytology screening program in BC in 2004. The centralized cervical cancer screening program (CCSP) processes every Pap smear carried out in BC at a single facility and all cytology results are stored in a database.

“DNA was isolated from 4980 of these samples and assessed for HPV prevalence and type distribution,” the authors noted. Results showed that the overall HPV prevalence in this large sample of women was 16.8%. “HPV prevalence was highest in the youngest group of women [ $<20$  years of age],” researchers reported. Out of all HPV-positive samples, 13.9% were positive for high-risk HPV, while 11.6% of the samples contained HPV types 16 or 18, which are targeted by both HPV vaccines. HPV 16 was the most common type identified, found in 10.7% of the samples—“higher than what is found in other Canadian and international studies,” investigators observed. They reported

that 52.3% of LGIL and 79.4% of HGIL contained high-risk HPV types while one-third of HPV-positive samples contained more than one HPV type.

Not unexpectedly, the prevalence of HPV 16 generally increased with the severity of abnormalities seen on cytology, being present in 8.7% of cytologically normal samples, in 35.2% of LGIL and in 52.4% of HGIL. All high-risk HPV types, including HPV 16 and 18, again showed a higher prevalence in samples with HGIL than in samples with LGIL, whereas the reverse was true for low-risk HPV types, including HPV 6 and 11. As the authors noted, this finding is consistent with previous observations that low-risk HPV types are less likely to be associated with progression to cervical cancer.

“This is the largest typing study of its kind in Canada to date and one of the largest single-centre studies worldwide,” investigators stated, “and while the HPV prevalence of screening women is not necessarily equivalent to that of all women in BC, the high participation rate of the CCSP—70%—argues that it provides a good estimate for the province.”

### Unmet need for influenza vaccine in older adults

Monto et al. *Influenza control in the 21st century: Optimizing protection of older adults*. *Vaccine* 2009;27(37):5043-53.

Currently available influenza vaccines do not offer optimal protection against influenza in older adults and there remains an unmet need for vaccines that provide both higher and broader protection against infection than those in use today.

Dr. Arnold Monto, University of Michigan School of Public Health, Ann Arbor, and international multicentre colleagues reviewed current and future strategies under evaluation that may address the currently unmet need in older adults who require better protection against influenza. According to the investigators, adjuvanted vaccines probably represent the best, most immediate strategy. “The MF59®-adjuvanted influenza vaccine provides older adults with greater seroprotection in the case of antigenic drift than non-adjuvanted vaccines and it is generally considered well tolerated.”

Another adjuvanted seasonal influenza vaccine currently in development uses a proprietary novel adjuvant system, AS03, and is currently undergoing phase III clinical trials. Studies

#### FEATURING SELECTED SUMMARIES FROM:

**Cancer Causes Control:** [www.springer.com/biomed/cancer/journal/10552](http://www.springer.com/biomed/cancer/journal/10552)

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**Sex Trans Dis:** [www.journals.lww.com/stdjournal](http://www.journals.lww.com/stdjournal)

**Clin Infect Dis:** [www.journals.uchicago.edu](http://www.journals.uchicago.edu)

**N Engl J Med:** [www.nejm.org](http://www.nejm.org)

to date indicate that cell-mediated immune responses to one of two different formulations of the AS03 proprietary vaccine were higher in older adults than in adults who received a non-adjuvanted vaccine; again, both formulations were considered well tolerated.

As investigators noted, virosomal vaccines represent a class of inactivated influenza vaccines that have the potential to enhance antibody response and induce cell-mediated immunity. Some studies do indicate that immune responses to virosomal vaccines are higher in older adults; yet others suggest that immune responses are inferior to those invoked by the MF59<sup>®</sup>-adjuvanted influenza vaccine. Using higher doses of the antigens in a vaccine is another strategy that has been shown to lead to significantly higher levels of seroprotection in older adults but discomfort rates do appear to increase as doses are increased. The benefit of live attenuated influenza vaccines has yet to be clearly demonstrated in older age groups.

DNA vaccines offer the potential for rapid production, do not require biosecurity and are not reliant on the supply of embryonated chicken-eggs, investigators pointed out, although only modest immunogenicity has been demonstrated in adult recipients of DNA vaccines. Recombination vaccines represent another novel method for vaccine production with early signs of promise. In addition, different modes of delivery may bolster the immune response to a vaccine. Intradermal vaccine delivery, for example, may enhance antigen presentation and findings to date suggest that intradermal delivery appears to be a viable alternative to the traditional vaccination route.

## Manitoba population findings show anogenital warts have high disease burden

*Kliwer et al. Twenty-year trends in the incidence and prevalence of diagnosed anogenital warts in Canada. Sex Transm Dis 2009;36(6):380-6.*

**P**opulation-based findings in Manitoba suggest that the incidence and prevalence of anogenital warts (AGWs) is higher among men than in women but that for both sexes, AGWs represent a substantial disease burden that could be largely prevented by timely vaccination with the quadrivalent human papillomavirus (HPV) vaccine.

Dr. Erich Kliwer, Cancer Care Manitoba, Winnipeg, and Canadian multicentre colleagues used population-based medical claims and hospital separation records to estimate the incidence and prevalence of AGWs in Manitoba between 1985 and 2004. “Approximately 25,000 Manitobans were diagnosed with AGWs between 1985 and 2004,” investigators stated, “and they experienced 29,882 episodes.” For both men and women, the annual age-standardized incidence rate peaked in 1992. Rates among males declined until 1999 but thereafter increased, they added. Rates among females also declined after 1991 but again started to increase in 2003.

Of interest, the incidence rate of AGWs increased between 1985 and 2004 for men in almost all age groups. As the authors suggested, men have had a higher incidence rate of AGWs than women since the year 2000. “In all years, women aged 20 to 24 had the highest incidence rate,” investigators noted, while for men, this was also true with the exception of the years 1997 to 1999, when men between the ages of 25 to 29 had the highest rate. Trends were similar for both the incidence and the prevalence rates of AGW in men and women.

AGWs do not generally warrant hospitalization, researchers commented, but 17% of all episodes of AGWs reported over the study interval required at least one hospitalization. One of the most consistently reported risk factors for AGWs is sexual behaviour—in particular, a greater number of partners. “It has been suggested that a changing sex ratio [in AGWs] may be a surrogate marker of changes in sexual behaviours among men who have sex with men,” investigators suggested, as not only is this population increasing in Canada, but riskier sexual practices also appear to be increasing: both may have contributed to the increasing incidence and prevalence of AGWs in men. The authors also note that AGWs have a substantial psychosocial impact on those infected.

“As such, AGWs not only represent a substantial burden to the health care system, but also to those infected and their prevention should be considered when setting goals of an HPV immunization program.”

## Over half of Hib vaccine failures likely unprotected against invasive disease over the long term

*Ladhani et al. Long-term immunological follow-up of children with Haemophilus influenzae serotype b vaccine failure in the United Kingdom. Clin Infect Dis 2009;49(3):372-80.*

**M**ore than one-half of children who developed invasive *Haemophilus influenzae* serotype b (Hib) disease despite having received the primary Hib vaccine series had antibody concentrations below levels believed to confer long-term protection some four years later. These findings suggest that Hib vaccine failures may be at further risk of invasive Hib disease and may benefit from an additional dose of the conjugate vaccine.

Dr. Shamez Ladhani, Centre for Infections, Health Protection Agency, London, UK, and multicentre colleagues determined Hib antibody concentrations in children who had invasive Hib disease any time after receipt of three doses of the conjugate vaccine given either in the first year of life, more than one week after receiving two doses of the vaccine given in the first year, or more than two weeks after receipt of a single dose of the vaccine given after the first year. “Of 323 families approached, 260 [80.5%] returned a completed questionnaire and 175 [54.2%] children provided a blood sample,” with approximately half of the samples being successfully analyzed, the authors reported. The

median age at follow-up was 8.4 years while the median duration of follow-up was 4.1 years.

Median anti-PRP levels (antibodies against the organisms' polysaccharide capsule) for all children was 0.70 µg/mL. Antibody levels were significantly lower for children with an underlying medical condition than for those without at 0.13 µg/mL vs. 0.81 µg/mL, researchers added. In addition, 56.9% of the cohort had antibody concentrations <1.0 µg/mL and 16.2% had concentrations of <0.15 µg/mL, "putative concentrations considered to provide long-term and short-term protection against Hib disease, respectively," investigators stated.

Indeed, over 40% of children who met the definition of vaccine failure had antibody concentrations of <0.15 µg/mL, almost the same proportion as children who had never received the vaccine. Moreover, when compared with age-related controls, children between the ages of 2 and 4 years had the lowest antibody concentrations in the overall cohort, to the point where >40% of children in this age group were not able to sustain adequate anti-PRP concentrations high enough to provide even short-term protection against invasive Hib disease.

"We report, to our knowledge, the largest and longest follow-up study of children with Hib conjugate vaccine failure," the authors stated, "and the finding that more than one-half of the children had antibody concentrations <1.0 µg/mL suggests that, perhaps, children with Hib vaccine failure are inherently unable to maintain long-term antibody-based immunity against Hib."

## Typhoid fever vaccine provides relatively high levels of protection

*Sur et al. A cluster-randomized effectiveness trial of Vi typhoid vaccine in India. N Engl J Med 2009;361(4):335-44.*

**T**he Vi typhoid fever vaccine has been shown to provide relatively high levels of protection both directly and through herd immunity, especially in children between 2 and 5 years of age who are most at risk for infection.

According to Dr. Dipika Sur, National Institute of Cholera and Enteric Diseases, Kolkata, India, and multicentre colleagues, the Vi vaccine has been given only sparsely in public health programs despite recommendations by the World Health Organization for its use in developing countries. "The limited use of the Vi vaccine in these settings has been partly due to doubts about the programmatic feasibility and effect of Vi vaccination in public health programs as well as questions about whether the vaccine is protective in children between the ages of 2 and 5 years and whether it can confer herd protection," researchers stated.

In a study designed to address all of these uncertainties, investigators carried out a large-scale, cluster-randomized trial in Kolkata, where typhoid fever is endemic. A total of 37,673 residents were vaccinated, 18,869 with the Vi vaccine and 18,804 with the hepatitis A control vaccine.

At two years' follow-up, typhoid fever had been diagnosed in 34 participants in the Vi vaccine group vs. 96 individuals in

the control vaccine group, for an overall level of effectiveness of 61%. When evaluated according to age at vaccination, the vaccine was found to be 80% protective in children under the age of 5 years, 56% protective among children between the ages of 5 and 14 and 46% protective among older vaccine recipients. Furthermore, the vaccine provided significant indirect protection against typhoid fever through herd immunity. Specifically, among unvaccinated residents in Vi vaccine clusters, the vaccine provided 44% protection against infection while the overall level of protection among all residents of Vi vaccine clusters was 57%. No serious adverse events attributable to either vaccine were observed during the month following receipt of the vaccine.

"Logistically and programmatically, it is possible to deliver the low-cost Vi vaccine in diverse settings in developing countries," the authors concluded, "and the fact that the adjusted level of overall protection was similar to the adjusted level of total protection among vaccinees, despite vaccine coverage of only about 60% of the subjects, underscores the importance of herd protection by the Vi vaccine."

## Decreased IPD incidence

*Kellner et al. Changing epidemiology of invasive pneumococcal disease in Canada, 1998-2007: Update from the Calgary-Area Streptococcus pneumoniae Research (CASPER) study. Clin Infect Dis 2009;49(2):205-12.*

**A** 10-year, population-based surveillance study was carried out in the Calgary Health Region (CHR) following the introduction of the universal, four-dose PCV7 infant vaccination program. Findings indicated a profound and sustained decrease in the incidence of invasive pneumococcal disease (IPD) due to PCV7 serotypes among vaccine-eligible children as well as among older children and adults.

Dr. James Kellner, Alberta Children's Hospital, Calgary, and multicentre colleagues determined the changing trends in IPD based on findings from the CASPER (Calgary Area Streptococcus pneumoniae Epidemiology Research) study, a prospective, population-based surveillance program of IPD among individuals of all ages in the CHR.

Over the 10-year surveillance interval, 1182 cases of IPD were reported in total. However, compared with the prevaccine period between 1998 and 2001, IPD incidence due to PCV7 serotypes during the vaccine period (2003 to 2007) decreased significantly (86%) in infants between the ages of 6 and 23 months, by 59% in 2- to 4-year olds, by 38% in those between the ages of 16 and 64, and by 78% in 65- to 84-year-olds. The total number of IPD cases also decreased between the two comparative intervals: by 77%, 45% and 34% in the three age groups, respectively. "The incidence of IPD due to non-PCV7 serotypes increased by 183%, and the total incidence of IPD increased by 73% among adults aged 16 to 64 years," investigators noted. However, they also explained, the increase in IPD incidence among this age group was primarily attributed to a large outbreak of serotype 5 IPD among homeless adults during 2005 and 2007. The number of cases due to most

other non-PCV7 serotypes was small, even though statistically significant increases in the incidence of overall cases due to serotypes 19A and 8 were seen during 2003 to 2007 compared with 1998 to 2001, they added.

“Since the introduction of PCV7 vaccine, there has been a profound decrease in the total number of cases of IPD among children and in cases due to PCV7 serotypes among subjects of all ages in Calgary, indicating a strong direct effect and herd effect of the vaccine,” investigators concluded, and while the serotypes that now cause IPD have changed significantly since then, “the magnitude and impact of replacement IPD caused by non-PCV7 serotypes is not yet known.”

## Inactivated influenza vaccine maintains protective antibody levels in infants under 6 months old

*Chiu et al. Immunogenicity and safety of intradermal versus intramuscular route of influenza immunization in infants less than 6 months of age: a randomized controlled trial. Vaccine 2009;27(35):4834-9.*

Vaccination with two doses of an inactivated trivalent influenza vaccine given either intramuscularly (i.m.) or intradermally (i.d.) was found to maintain protective antibody titres in infants who received the vaccine at 2 to 3 months of age.

Dr. Susan Chiu, The University of Hong Kong, China, and colleagues carried out a randomized trial comparing i.m. and i.d. administration of an inactivated trivalent influenza vaccine in 126 infants who received the vaccine between the ages of 2 and 3 months. “Two doses four weeks apart were administered,” they noted, “and the dose of 0.25 mL is the same as that recommended for infants 6 to 35 months of age.” Because the presence of maternal antibodies could confuse the seroprotection rate, investigators used a fourfold rise in antibody titres to at least one of the influenza antigens as an

end point. Prior to vaccination, only four infants out of the 126 in the study had hemagglutination inhibition (HAI) titres <40 against one or more vaccine-covered antigens. Levels <40 are considered inadequate for protection against influenza infection.

Following vaccination, there was no difference in the fold-rise of HAI titre response in infants who received the vaccine i.m. or i.d. and HAI titres above seroprotective levels (i.e. at least 40) against all three vaccine antigens were maintained in 97.6% of the infants, regardless of the vaccination method used.

“We demonstrated that i.m. and i.d. vaccination of infants as young as 2 months old using the dosages and regimen in this study is safe,” the authors concluded, “so contrary to conventional wisdom, this study demonstrated that in the face of maternal HAI titres, vaccination with the inactivated trivalent influenza vaccine via both the i.m. and i.d. routes serves to maintain titres above protective levels in infants under 6 months of age.” □

### UPCOMING EVENTS

#### **6th European Congress on Tropical Medicine and International Health**

September 6-10, 2009 / Verona, Italy

#### **3rd Vaccine Global Congress**

October 4-6, 2009 / Bangkok, Thailand

#### **American Academy of Pediatrics (AAP) National Conference**

October 17-20, 2009 / Washington, DC

#### **Travel Medicine Update 2009**

November 14, 2009 / Toronto, Ontario

#### **6th World Congress of the World Society of Pediatric Infectious Diseases**

November 19-22, 2009 / Buenos Aires, Argentina

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