

VACCINE

RESOURCE LINE

A BIMONTHLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

Protecting Canadian adults from vaccine-preventable diseases: NACI recommendations

Parkins et al. Routine immunization of adults in Canada: Review of the epidemiology of vaccine-preventable diseases and current recommendations for primary prevention. Can J Infect Dis Med Microbiol 2009;20(3):e81-e90.

Morbidity and mortality from vaccine-preventable diseases now occur disproportionately in adults and every effort must be made to protect adults against diseases from which an estimated 30,000 to 50,000 North Americans die each year. Dr. Michael Parkins, University of Calgary, Alberta, and multicentre colleagues reviewed current recommendations for routine immunization of adults in Canada by the National Advisory Committee on Immunizations (NACI).

- **Tetanus and diphtheria prevention:** All children and adults should be vaccinated against tetanus and diphtheria. Booster doses of adsorbed tetanus and diphtheria toxoids delivered as Td are recommended every 10 years throughout adulthood. Adult Canadians who may not have received a primary tetanus immunization series (immigrants/refugees) require three doses—the first two separated by at least four weeks, and a third dose six to 12 months later.
- **Pertussis prevention:** All adults who have not previously had a dose of acellular pertussis should receive a single dose, given with a routine Td booster in the combination form Tdap in place of Td. Tdap can also be given to adults with specific need (contact with infants) within two years

of receipt of Td without significant risk of adverse effects; shorter intervals may be used. Pregnant women should only be given when benefits outweigh risks.

- **Measles, mumps, rubella prevention:** All Canadians should have immunity to MMR, as adults born before 1970 can be presumed to have had prior natural exposure. Those born after 1970 without a documented history of immunity should receive a single dose of the MMR vaccine. Adults born after 1970 perceived to be at increased risk for MMR infection should receive a second dose as a booster. The MMR vaccine should not be administered to pregnant women or individuals with inherited or acquired immunodeficiencies.
- **Varicella prevention:** All susceptible adults without contraindications to the varicella vaccine should receive two subcutaneous doses separated by four to eight weeks. Absolute contraindications to vaccination include advanced immune suppression and pregnancy. Vaccines approved in Canada for prevention of primary varicella disease are not approved for the prevention of recurrent varicella disease. For the prevention of herpes zoster and postherpetic neuralgia, the herpes zoster vaccine has been approved and is recommended for individuals 60 years of age and older.
- **Invasive pneumococcal disease prevention:** The polysaccharide vaccine should be given to adults at highest risk, including individuals with chronic medical conditions, residents of long-term care facilities and all those 65 years of age and older. Homeless persons and injection drug users should also receive the vaccine. Protective antibody levels fall five to 10 years after receiving the vaccine and repeated dosing is occasionally indicated in the highest risk groups.
- **Influenza prevention:** NACI recommends routine adult immunization in four specific groups of adults: a) those at increased risk of influenza-related morbidity and mortality; b) those at increased risk of propagating influenza to high-risk patients; c) those providing essential community services; d) workers culling poultry infected with avian influenza.

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“Ensuring optimal immunization of Canadians through adulthood is important not only to reduce the burden of morbidity, mortality and healthcare expenditures for vaccine-preventable diseases in this population, but also to reduce the number of susceptible hosts, thereby providing additional protection to those groups at highest risk,” the authors emphasized.

HPV vaccination a cost-effective cervical cancer prevention strategy

Prasad SR. *Management strategies and cost effectiveness in the prevention of cervical cancer*. ClinicoEconomics and Outcomes Research 2009;1:17-23.

Vaccination against human papillomavirus (HPV) is a cost-effective cervical cancer prevention strategy, according to a review of the evidence by Dr. Smita R. Prasad, University of Kentucky, College of Public Health, Lexington.

Dr. Prasad examined cost-effectiveness strategies now used in cervical cancer prevention, including primary prevention with the HPV vaccine and secondary prevention with screening programs. “In unscreened populations alone, introduction of screening programs has demonstrated significant reductions in cervical cancer rates by 60% to 90% within three years of screening instigation,” he reported, “[but] screening alone is not sufficient to maximize cervical cancer prevention.”

In reviewing four previously published studies in which the potential cost-effectiveness of the HPV vaccine was estimated, the authors determined that the cost of vaccination compared to no vaccination ranged from \$22,800 (US) per quality-adjusted life year (QALY) in 2001 dollars to \$24,300 per QALY in 2002 dollars. Other analyses estimated the cost-effectiveness of HPV vaccination at between \$14,600 per QALY in 2001 dollars and \$3,000 per QALY in 2005 dollars.

“Few cost:benefit analyses on the HPV vaccine are available,” Dr. Prasad noted. Cost:benefit analyses attribute monetary value to both costs and benefits while cost-effectiveness analyses only monetize the costs of a program and not the benefits. However, one cost:benefit analysis involving Medicaid-enrolled females in the Appalachian region of Kentucky found that using the HPV vaccine as a primary prevention strategy was, indeed, cost-saving when the rising cost of healthcare, the aging population and the cost of treating cervical cancer were taken into account.

“The costs to treat cervical cancer cases in nonvaccinated females and the costs to maintain screening programs would still be incurred,” Dr. Prasad observed. “However, consideration of the fact that the HPV vaccine will also decrease incidence of anogenital warts and other associated HPV diseases in addition to thwarting the need for diagnosis, treatment and surgical intervention of these ailments is important to acknowledge and may offset additional costs.”

Adjuvanted influenza vaccine induces better immune responses than non-adjuvanted vaccine in young children

Vesikari et al. *Enhanced immunogenicity of seasonal influenza vaccines in young children using MF59 adjuvant*. *Pediatr Infect Dis J* 2009;28(7):563-71.

An adjuvanted influenza vaccine has been shown to induce significantly greater, longer-lasting and broader immune responses in children from the ages of 6 months to <36 months of age than a nonadjuvanted split vaccine, with both vaccines having comparable tolerability.

Dr. Timo Vesikari, University of Tampere Medical School, Finland, and colleagues compared the immunogenicity, clinical tolerability and safety of primary and booster doses of an MF59-adjuvanted inactivated influenza subunit vaccine to a conventional nonadjuvanted split vaccine in healthy children. In the primary trial, 269 children received at least one dose of vaccine; 130 in the Sub/MF59 group and 139 in the split group. Smaller numbers of children were enrolled in the extension study where they received a booster dose one year after the primary inoculation.

“Overall, postvaccination geometric mean titres [GMTs] and geometric mean ratios [GMRs] were significantly higher with Sub/MF59 than with the split vaccine for all three vaccine virus strains,” investigators reported. In the total population, both vaccines elicited comparably high seroprotection rates against A/H3N2 at 100% with the adjuvanted vaccine vs. 99% with the split vaccine.

Conversely, the adjuvanted vaccine elicited significantly higher seroprotection rates against A/H1N1 at 100% compared with 86% for the split vaccine following two doses which are recommended for this age group. After a single dose of each vaccine, the authors also noted that a significantly greater proportion of infants receiving the Sub/MF59 vaccine achieved protective antibody levels against A/H3N2 at 91% compared with 49% following the split vaccine, as well as against A/H1N1 at 51% seroprotection rates compared with 18% with the split vaccine.

“Antibody responses to influenza B remained low after a single dose in both vaccine groups,” the authors added, “however, after two doses, 99% of subjects in the Sub/MF59 group had seroprotective levels of... antibody compared with only 33% of subjects in the split vaccine group.” The most marked differences in seroprotective antibody levels were observed in children between 6 and 11 months, with 100% of children in this age group who received the adjuvanted vaccine achieving seroprotective levels compared with only 12% of those who received the split vaccine. The adjuvanted vaccine did result in slightly higher levels of local reactogenicity, but had similar systemic reactogenicity compared with the conventional influenza vaccine. Both vaccines demonstrated comparable safety profiles following a booster dose given one year after the first dose.

“This is the first study of MF59-adjuvanted subunit influenza vaccine in young children,” researchers concluded, “and the FM59 adjuvant demonstrated that it can significantly increase the immune response in young children against all seasonal influenza subtypes.”

Higher immune responses predict less severe herpes zoster infection in the elderly

Weinberg et al. *Varicella-zoster virus-specific immune responses to herpes zoster in elderly participants in a trial of a clinically effective zoster vaccine*. *J Infect Dis* 2009;200(7):1068-77.

According to multicentre trialists involved in the Shingles Prevention Study (SPS), higher varicella-zoster virus (VZV) cell-mediated immunity (CMI) responses in elderly patients with herpes zoster (HZ) predicts a less severe course of HZ infection and lower risk of patients developing postherpetic neuralgia (PHN). In contrast, higher antibody titres were associated with increased HZ severity and a greater risk of patients developing PHN, the same investigators concluded. Both active infection with HZ and the HZ vaccine generated comparable VZV CMI responses.

Dr. Adriana Weinberg, University of Colorado, Denver, and fellow SPS investigators evaluated the association between VZV-specific humoral and CMI responses to HZ and protection against HZ morbidity among 981 elderly persons—321 vaccinees and 660 placebo recipients—who developed HZ during the SPS study. Responses were compared to 1362 without HZ, consisting of 682 who received the active vaccine and 680 placebo recipients.

Investigators observed that a robust VZV CMI response at the onset of HZ infection correlated with reduced morbidity, whereas VZV antibody titres did not. “Three weeks after HZ onset, gpELISA titres were highest in those with more severe HZ and were slightly increased in placebo recipients compared with zoster vaccine recipients and in older individuals,” researchers added. They also pointed out that the lack of a protective effect of VZV-specific antibodies against HZ severity might seem to contradict the correlation between antibody responses to the HZ vaccine and protection against the incidence of HZ.

“However, a unifying hypothesis is that antibody titres increase in response to VZV antigenic stimulations, resulting either from zoster vaccine or from HZ,” they noted. In the case of HZ, the extent of VZV replication determines both the severity of the disease and the magnitude of the antigenic stimulation, whereas with the zoster vaccine, limited replication of the less pathogenic live, attenuated virus is insufficient to cause disease in seropositive recipients but still sufficient to induce VZV antibody and CMI responses.

“This study showed that greater VZC CMI responses in the first week after HZ rash onset... correlated with decreased severity of disease and with lower occurrence of PHN, suggesting a protective effect of CMI against the morbidity of HZ,” investigators concluded. They added that higher levels of VZV

CMI responses at early time points were more important for protection against HZ and PHN than the magnitude of peak responses.

Pain following HPV vaccine less frequent, severe than with other adolescent vaccines

Reiter et al. *How much will it hurt? HPV vaccine side effects and influence on completion of the three-dose regimen*. *A. Vaccine* 2009 Sep 15 [Epub ahead of print].

Pain experienced by young recipients of the human papillomavirus (HPV) vaccine is reported to be less frequent and less severe than that associated with other adolescent vaccines and did not affect completion of the HPV regimen among survey participants, according to the first study of its kind in which the side effects of the vaccine were specifically evaluated.

Dr. Paul Reiter, University of North Carolina Gillings School of Global Public Health, Chapel Hill, and multicentre colleagues polled parents for their daughters’ experience with pain and syncope following HPV vaccination and compared it to their experience following receipt of other adolescent vaccines. A total of 889 parents completed baseline interviews and 650 completed follow-up interviews. The report included cross-sectional data from 229 parents who reported that their daughters had received one or more doses of the HPV vaccine.

Some 65% of the parents interviewed reported that their daughters experienced pain or discomfort following receipt of the HPV vaccine, more commonly at the time of injection (58%) than in the hours and days following vaccination (45%). However, very few parents reported that their daughters experienced moderate (10%) or severe (2%) pain at the time of injection or in the hours or days following vaccination, investigators noted. “No parents reported syncope among their daughters following HPV vaccination,” they stated, although a few parents indicated their daughters felt light-headed or dizzy after vaccination. Importantly, among those parents whose daughters had received both the HPV vaccine and a tetanus booster, daughters were more likely to report a lower level of pain from the HPV vaccine than from the tetanus booster. Similarly, parents of daughters who had received both the HPV vaccine and the meningococcal vaccine were more likely to report a lower level of pain from the HPV vaccine than from the meningococcal vaccine, investigators confirmed.

Reported pain from HPV vaccination also did not influence timely uptake of subsequent doses of the HPV vaccine, as parents of daughters who had completed the three-dose series (or were within recommended time guidelines to do so) reported pain or discomfort at the time of injection (62%) nearly as often as parents whose daughters were late for their second or third dose (68%).

“To our knowledge, this study is the first to examine HPV vaccine-related pain outside the context of a clinical vaccine

efficacy trial,” investigators concluded, “and such information can help alleviate concerns and fears regarding adverse events following HPV vaccination not only among parents but also healthcare providers, as both groups have expressed concern over possible side effects from the vaccine.”

Monovalent HPV-16 vaccine remains 100% effective through 8.5 years of follow-up

Rowhani-Rahbar et al. Longer term efficacy of a prophylactic monovalent human papillomavirus type 16 vaccine. Vaccine 2009;27(41):5612-9.

Administration of the monovalent human papillomavirus (HPV) type 16 L1 virus-like particle vaccine has demonstrated 100% efficacy against infection with HPV type 16 and remained effective through 8.5 years of follow-up.

Dr. Ali Rowhani-Rahbar, University of Washington, Seattle, and colleagues conducted an extended follow-up study to assess the longer-term efficacy of a monovalent HPV-16 vaccine against infection as well as against HPV-16-related cervical intraepithelial neoplasia (CIN) among a proportion of women who had participated in a randomized control trial of the same vaccine 8.5 years earlier. “Between October 1998 and November 1999, 2391 women participated in a multicentre, double-blind, phase IIb, randomized, controlled trial of a monovalent HPV-16 vaccine in the US,” the authors explained.

Approximately 500 of these women were enrolled in Seattle, half of whom received the vaccine and the other half placebo. In February 2006, the same 500 were asked to participate in an extended follow-up study to assess the longer-term efficacy of the monovalent HPV-16 vaccine. A total of 291 of these women were enrolled in the extension study between March 2006 and May 2008. The mean follow-up since enrolment in the original trial was 8.5 years (range, 7.2 to 9.5 years) and a total of 114 of the cohort completed the third visit, the majority of the visits occurring between years 8 and 9 of follow-up. “During the extended follow-up period, no woman was found to be infected

with HPV-16 in the vaccinated group,” the authors reported, for a vaccine efficacy of 100%. Among placebo recipients, two women were infected with HPV-16 at their first study visit.

As also revealed from the extended follow-up period, no woman in the vaccine group developed HPV-16-related CIN compared with three women in the placebo control, for a 100% vaccine efficacy. As investigators noted, immunogenicity analysis showed that serum HPV-16 antibody levels had only slightly decreased since month 48 post-enrolment in the original trial among vaccine recipients. At an average follow-up of 8.5 years, the geometric mean titre of serum HPV-16 antibody was significantly higher in the vaccine group than among placebo controls. A significantly higher proportion of vaccine recipients were HPV-16-seropositive than placebo controls as well.

“To our knowledge, this study provides information on efficacy and immunogenicity after the longest duration of follow-up for any prophylactic HPV L1 VLP vaccine,” researchers stated, “and the results of this study suggest that 8.5 years after its administration, the monovalent HPV-16 vaccine remains efficacious and immunogenic.” □

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