Spring 2012

VACCINE RESOURCE LINE

A QUARTERLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

Chief Medical Editor: Dr. Léna Coïc, Montréal, Quebec

NACI: New recommendations for the quadrivalent HPV vaccine for males

National Advisory Committee on Immunization. Canada Communicable Disease Report *January 2012;38:ACS-7.*

Recommendations for the use of the quadrivalent human papillomavirus (HPV) vaccine have now been extended to males between the ages of 9 and 26 for the prevention of anal intraepithelial neoplasia (AIN) of all grades, anal cancer and anogenital warts (AGWs).

The evidence upon which the National Advisory Committee on Immunization (NACI) based the new recommendation was judged to be as strong (Grade A) as their previous recommendation to administer the same vaccine to females in the same age group. "When NACI makes a recommendation, it becomes standard of care," Dr. Vivien Brown, President (Toronto branch), Federation of Medical Women of Canada (FMWC), stated in her comments on the new recommendations. The FMWC recently called on provincial and territorial governments to provide funding for the vaccination of boys against HPV as part of current school-based vaccination programs. "There is clear evidence the vaccine reduces cancer risk," Dr. Brown added, "and it is therefore only fair and equitable that men and boys have access to a recommended vaccine."

NACI also indicated that either the quadrivalent or bivalent vaccine may be given to females over the age of 26 years. However, efficacy data have only been demonstrated for the quadrivalent vaccine in females between the ages of 27 and 45 and not for the bivalent vaccine; consequently, NACI graded their recommendation for the bivalent vaccine as "B" as opposed to "A" evidence for the quadrivalent vaccine.

In the same updated statement, NACI also recommended males who have sex with males (MSMs) receive the quadrivalent vaccine from the age of 9 onwards. In contrast, NACI did not recommend males receive the bivalent vaccine as efficacy end points in males receiving the bivalent vaccine are lacking. In considering the inclusion of males in existing female-only routine HPV immunization programs, NACI suggested that governments consider the public health and economic burden that AGWs alone represent today, over 90% of which are caused by HPV 6 and 11. Among men, for example, Canadian studies indicate that the incidence of AGWs in men ranges between 131 and 154 per 100,000 men depending on the province and the year.

Incidence rates of AGWs have also been increasing among males compared to females in recent years. The mean length of an AGW episode was estimated to be 76 days for men in one British Columbia-based study vs. 61 days for women, at an average treatment cost per episode of about $190. From a patient's perspective, investigators have also reported that a first episode of AGWs produces a quality-adjusted year loss equivalent of 9 to 40 days of healthy life lost.

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Postpartum pertussis immunization does not prevent infection in young infants

Castagnini et al. Impact of maternal postpartum tetanus and diphtheria toxoids and acellular pertussis immunization on infant pertussis infection. CID *2012;54:78-84.*

According to a Texas-based study, immunizing postpartum mothers with the tetanus/diphtheria/pertussis (Tdap) vaccine does not reduce pertussis illness in infants 6 months of age and under. Efforts must still be directed at immunizing all household members and key contacts of newborns to protect the vulnerable young.

Dr. Luis Castagnini, Baylor College of Medicine, Houston, and multicentre colleagues carried out a cross-sectional study in which they compared 2 time intervals: pre-intervention between July 2000 through to December 2007 and post-intervention from January 2008 through to May 2009. "The intervention was a routine standing order for maternal postpartum Tdap immunization at the Ben Taub General Hospital (BTGH), Houston, Texas," the authors noted, "and from January 2008 through May 2009, 5223 of 7782 (67%) postpartum women received Tdap."

As the authors reported, 664 infants ≤6 months of age were diagnosed with *Bordetella pertussis/Bordetella parapertussis* during the entire study period. "Overall, 514 infants had laboratory-confirmed pertussis during the study period," they recorded, 378 (73.5%) in the pre-intervention period and 136 (26.5%) in the post-intervention period. The mean age at diagnosis for all infants was 77 days; infants who developed pertussis were similar in age at diagnosis, sex, hospital of diagnosis, severity of illness and

outcome during the 2 interludes examined. The proportion of infants of Hispanic ethnicity who developed pertussis was higher in the post-intervention period than in the pre-intervention interval but as the authors pointed out, Hispanic infants have "substantially higher rates" of pertussis-associated complications and death than infants of other ethnicities.

After adjusting for age, sex, and ethnicity, however, "the proportion of pertussis-infected infants born at the BTGH and potentially protected through maternal postpartum Tdap immunization were similar for the 2 periods," the authors stated, at 6.9% vs. 8.8% pre- and post-intervention intervals, respectively.

"This study describes, to our knowledge, the first critical evaluation of a recommended public health strategy that is specifically targeted toward preventing pertussis among infants too young to have completed their primary TDaP immunization series," the authors stated. They noted that their findings, although disappointing, were not surprising, given the likelihood that infants had contact with other pertussis-infected individuals.

Mass rotavirus vaccination program could eliminate RVGE in young children

Atkins et al. Impact of rotavirus vaccination on epidemiological dynamics in England and Wales. Vaccine *2012;30:552-64.*

Introduction of a mass rotavirus pentavalent vaccination program in England and Wales could reduce the annual incidence of severe rotavirus gastroenteritis (RVGE) by over 70% if vaccine immunity lasts only as long as the duration of a natural infection, but could eliminate severe RVGE in children under the age of 5 years if vaccine immunity lasts for at least 3 years.

Dr. Katherine Atkins, Yale School of Public Health, New Haven, Connecticut, and multicentre colleagues simulated the impact of rotavirus vaccination on the incidence of rotavirus infection in England and Wales following mass vaccination of vaccine-eligible infants from early October 2011. "If birth rates remain constant, mass vaccination can reduce the annual incidence of severe RVGE by around 72% (and overall RVGE by around 68%) of its pre-vaccination levels if vaccination is effective for a mean duration of one year," investigators stated. However, if immunity from the pentavalent rotavirus vaccine does not wane for at least 3 years, "elimination of all RVGE for the under-5-year-old population could occur before or during the second year post-intervention under all parameter scenarios," they added.

Where vaccination does not lead to elimination of disease in young children, severe RVGE cases would still drop from approximately 16,500 cases per week to around 3000 per week, whereas any RVGE episode would drop from 69,000 cases to 14,000 per week. Assessing the impact of the same vaccine on herd immunity over a 20-year period, investigators also calculated that indirect effects of mass vaccination would account for approximately 25% of the total reduction in the incidence of severe RVGE when vaccine immunity lasts for a mean of 1 year. However, if there is no waning of immunity in the first 3 years of life, "direct effects alone predict around a 92% reduction in severe RVGE and a 45% reduction for any RVGE; if indirect effects are also taken into account, the elimination of all RVGE in children less than 5 years of age is predicted," investigators stated.

The same model also predicted that the mass vaccination program would delay the rotavirus epidemic peak by about 2.5 months with 95% coverage.

American varicella vaccination program has significant indirect benefits on infants not eligible for vaccination

Chaves et al. Varicella in infants after implementation of the US varicella vaccination program. Pediatrics *2011;128:1071-7.*

The varicella vaccination program, introduced in the US in 1995, has led to dramatic indirect benefits for infants not eligible for vaccination, according to a large-scale, community-based surveillance project tracking the epidemiology of varicella from 1995 to 2008.

Dr. Sandra Chaves, Centers for Disease Control and Prevention, Atlanta, Georgia, and multicentre colleagues examined 14 years of data to describe the epidemiology and clinical presentation of varicella disease in infants since the vaccination program's introduction in 1995. The authors reported that varicella incidence among infants younger than 12 months declined 89.7% from 15.6 cases per 1000 infants in 1995 to 1.6 cases per 1000 infants in 2008. "The decline inversely followed an increase in varicella vaccination coverage."

Prior to the introduction of the vaccination program, incidence of varicella was highest among children between the ages of 1 and 10 years, followed by infants and adolescents aged 10 to 14 years. By 2008, "disease incidence was similar in all age groups," investigators noted. Statistically significant differences were also seen in the clinical presentation of varicella among infants: those between 0 and 5 months had generally milder disease compared with infants aged 6 to 11 months. A lower proportion of the youngest infants also had ≥50 lesions; fewer had fever >38° C; fewer had varicella-related complications; and fewer were prescribed antibiotics compared to the older infants. The authors suggested that the presence of maternal varicella-zoster virus antibodies might explain attenuated disease in very young infants likely born to mothers with a history of varicella.

The most frequently reported complications from varicella in the survey were skin superinfection followed by otitis media and diarrhea. Only 15 infants required hospitalization for varicella across the entire survey, two-thirds of them being infants between 6 and 11 months.

"This study is the first community-based investigation of the detailed epidemiology and clinical characteristics of varicella among infants after implementation of a national varicella vaccination program," the authors stated. "The benefit [from this program] reinforces the importance of maintaining high rates of varicella vaccination in the community to protect individuals who cannot be vaccinated because of age or medical contraindications."

CKD patients with vitamin D deficiency poor responders to hepatitis B vaccine

Zitt et al. Vitamin D deficiency is associated with poor response to active hepatitis B immunization in patients with chronic kidney disease. Vaccine *2012;30:931-5.*

Patients with chronic kidney disease (CKD) and vitamin D deficiency have a poor response to hepatitis B vaccination with a low proportion of them achieving seroprotective levels against the virus following vaccination.

Dr. Emanuel Zitt, Academic Teaching Hospital Feldkirch, Austria, and colleagues carried out a retrospective analysis of approximately 200 CKD patients who had received the hepatitis B vaccine between 2005 and 2010. None of the patients were on immunosuppressive therapy at the time. Patients received 3

doses of the hepatitis B vaccine at 0, 1 and 6 months, in accordance with CDC guidelines. "Of the 200 patients, only 5 had a 25(OH)D level within the normal range (>30 ng/mL)," the authors reported, "and vitamin D deficiency, defined as a level of <10 ng/mL, was observed in 35.5% of the patients."

As investigators also noted, vitamin D deficiency was more prevalent in dialysis patients than in predialysis patients while patients with diabetes also had significantly lower 25(OH)D levels (11.7 ng/mL) than nondiabetic patients (15.2 ng/mL). Seroconversion rates were also lower in patients with diabetes (approximately 42%) compared with those without diabetes (approximately 62%).

As investigators also recorded, 57% of the overall cohort were able to mount an antibody response ≥100 IU/L but seroprotective levels where antibody titres reached 100 IU/L or greater was observed in only 35% of the study group; 43% of patients had no response to the hepatitis B vaccine at all. Non-responders had significantly lower 25(OH)D levels than patients who seroconverted as well. Slightly over half of the cohort was also treated with a vitamin D receptor activator such as calcitriol, but there was no difference in the seroconversion rate between those who were treated and those who were not.

"Based on our results, we speculate that treatment of vitamin D deficiency prior to hepatitis B vaccination might... be a simple and cheap means of achieving seroconversion and strong immune response with long-term seroprotection," the authors suggested. They cautioned, however, that this hypothesis would need to be tested in a prospective randomized trial before implementing vitamin D supplementation prior to immunization.

Quadrivalent conjugate meningococcal vaccine well tolerated, immunogenic when given together with routine infant vaccines

Klein et al. Safety and immunogenicity of a novel quadrivalent meningococcal CRM-conjugate vaccine given concomitantly with routine vaccinations in infants. Pediatr Infect Dis J *2012;31: 64-71.*

Results from a pivotal phase III trial evaluating the safety and immunogenicity of the MenACWY-CRM conjugate vaccine, given concomitantly with routine vaccinations in infants, has reaffirmed its immunogenicity and that it is well tolerated in young infants. The vaccine can also be co-administered with routine infant vaccines at 2, 4 and 6 months of age with no compromise in immunogenicity.

For the study, 1508 full-term infants were randomized to 4 doses of the MenACWY-CRM vaccine at 2, 4, 6 and 12 months of age either concomitantly with routine vaccinations or to routine vaccinations alone. Immune responses to 4 doses of the MenACWY-CRM vaccine were also compared to those elicited after a single dose of the same vaccine given at 12 months of age. The concomitant vaccines given during the study included the combined DTaP-HBV-IPV; a DTaP booster; Hib-TT; PCV7; a rotavirus vaccine; or MMRV.

Investigators obtained serum samples before and 1 month after the infant series at 2 and 7 months of age and before and 1 month after the 12-month toddler dose at 12 and 13 months of age. Functional antibodies to each meningococcal serogroup were measured using the hSBA assay. Immunogenicity was measured as the percentage of infants with hSBA titres ≥8 against each serogroup 1 month after the fourth doses as well as by geometric mean titres. Of the 1508 infants enrolled, 479 were enrolled into the immunogenicity cohort and the remaining 1029 were enrolled into the safety-only cohort.

One month after the third dose of the MenACWY-CRM vaccine, 67% the of infants had achieved hSBA titres ≥8 against serogroup A; 97% against serogroup C; and 96% against both serogroup W-135 and Y. Prior to receipt of the fourth dose, these levels did wane, although 52% to 69% of MenACWY-CRM recipients still maintained hSBA titres ≥8 against serogroups C, W-135 and Y after 3 doses. However, 1 month after the fourth dose (given at 12 months of age), 100% of infants had achieved hSBA titres ≥8 against serogroups W-135 and Y, while 94% had achieved the same protective antibody levels against serogroup A and 98% against serogroup C.

One month after infants had received the primary infant series, investigators also observed seroresponse rates that were non-inferior among MenACWY-CRM recipients for diphtheria, tetanus, HBV, Hib antigens and for all poliovirus serotypes compared with infants who received routine vaccination alone. Non-inferiority was demonstrated for all pertussis antigens as well, as were seroresponses for all pneumococcal serotypes except for PnC6B. One month after infants received the fourth PCV7 dose at 12 months, non-inferiority was achieved for all PCV7 serotypes.

Adverse event rates were similar among those infants who received the meningococcal vaccine with concomitant routine vaccines at 75% and those who received routine vaccination alone at 76%. Interestingly, after the fourth dose of the meningococcal vaccine, the adverse event rate was lower among infants who received the MenACWY-CRM vaccine along with routine vaccines at 55% compared with infants who received routine vaccines alone at 62%.

The vaccine was also well tolerated with local reactogenicity rates comparable to those seen following routine vaccines alone.

Catch-up HPV immunization of females would be cost-effective in Canada

Tully et al. Time for change? An economic evaluation of integrated cervical screening and HPV immunization programs in Canada. Vaccine *2012;30:425-35.*

Catch-up immunization of females with the bivalent human papillomavirus (HPV) vaccine—either through a school-based program or a clinic-based program—could be cost-effective in the Canadian setting, according to an economic evaluation of integrated cervical screening and HPV immunization programs in Canada.

Moreover, the combined strategy of implementing catch-up immunization and delaying initial screening for cervical cancer was also predicted to save costs and generate significant gains in quality-adjusted life-years (QALYs). The most cost-saving strategy—which would also be the most effective in reducing the incidence of squamous cell carcinoma (SCC) and augmenting gains in QALYs—would be to implement a clinic-based catch-up program in females between the ages of 13 and 26 while simultaneously delaying initial cervical cancer screening until the age of 25.

Stephen Tully, PhD, University of Guelph, Ontario, and multicentre investigators carried out an economic evaluation of catch-up immunization programs in older females, starting cervical screening at a later age than current practice recommendations and possible combinations of these 2 strategies in a population where a universal HPV immunization program of pre-adolescent females was already in place. "We assumed use of the bivalent

vaccine which has a high efficacy (>90%) against incident and persistent type 16/18 infections," they noted, "and our baseline school-based immunization program was assumed to cover 80% of 12-year-old females with 3 doses of bivalent HPV vaccine."

Firstly, the model predicted that a school-based program where 80% of females are immunized at the age of 12 would be cost-effective compared to no immunization, yielding an incremental cost-utility ratio below a threshold of $50,000 QALY. A baseline school-based program combined with school-based catch-up immunization was also found to be cost-effective compared to no immunization at the same threshold. Furthermore, "both the clinic-based catch-up program and the school-based catch-up program are cost-effective compared to no catch-up in the presence of a baseline school-based immunization program," investigators added. And in the presence of the latter, "delaying the initial screening age to either 21 or 25 results in significant cost savings compared to current screening practices," they added.

However, delaying initial cervical cancer screening until age 21 or 25 may not result in net QALY gains if the harm of preventing slightly fewer cases of cervical cancer in these age groups outweighs the benefits of avoiding numerous false-positives; the combined strategies may also result in a small increase in SCC incidence.

The clinic-based catch-up program in women 13 to 26 years of age while simultaneously delaying initial cervical cancer screening until the age of 25 proved to be most cost-effective because it would stop screening in an age group that is at low risk for SCC, the authors explained. The same strategy would also be "highly effective" because it would expand vaccine coverage in younger age groups that are no longer screening, and herd immunity protection would compensate for lower vaccine coverage compared to the school-based catch-up program.

The model included herd immunity effects, vaccine cross-protection against HPV types not contained in the vaccine and the most recent information on reduced cost of the bivalent vaccine, all of which have a significant impact on predicted cost of QALY gained.

Second dose of zoster vaccine safe, but not more immunogenic than initial dose

Joost Vermeulen et al. Safety, tolerability and immunogenicity after 1 and 2 doses of zoster vaccine in healthy adults ≥60 years of age. Vaccine *2012;30:904-10.*

According to a multicentre study, a second dose of the herpes zoster vaccine is safe for healthy adults 60 years of age and older but it does not enhance immunogenicity over that produced by a single dose.

Dr. Joost Vermeulen, University of Amsterdam, The Netherlands, and multicentre colleagues randomized 210 individuals ≥60 years of age to 2 doses of the zoster vaccine (ZV) separated by 6 weeks or to placebo. Mean age at enrolment was 68.7 years for the vaccine group and 70.7 years for placebo controls; almost half were at least 70 years of age and older. "Immunogenicity was evaluated using VZV (varicella-zoster virus) interferon-gamma (IFN-gamma) enzyme-linked immunospot (ELISPOT) assay and VZV glycoprotein enzyme-linked immunosorbent antibody (gpELISA) assay," investigators noted. Blood samples were obtained immediately prior to vaccination and 2 and 6 weeks after each dose while adverse events were recorded on a standardized vaccination report card.

As the authors reported, the VZV IFN-gamma ELISPOT geometric mean count (GMC) among vaccine recipients rose from 16.9 spot-forming cells per 106 peripheral blood mononuclear cells prior to vaccination to 49.5 2 weeks after the first dose, after which they declined to 32.8 some 6 weeks after receipt of the first dose. After the second dose, the GMC of the same ELISPOT response was 44.3 at 2 weeks, 42.9 after 6 weeks and 36.5 at 6 months. The VZV response measured by the gpELISA geometric mean titres were higher in the vaccine group than in the placebo controls at 6 weeks following each dose of the vaccine, but correlation between IFN-gamma ELISPOT findings and the gpELISA assay was poor.

In contrast, immunologic measurements remained unchanged in placebo controls. The safety profile of the herpes zoster vaccine after each dose was similar to that determined in the Shingles Prevention Study, as was the immunogenicity profile. Investigators noted that these results "[provided] reassurance that multiple doses of the ZV can be administered without substantially increasing the risk of adverse experiences [even though] there is no apparent immunologic advantage of a second dose of the ZV administered shortly after an initial dose."

The investigators indicated that the potential impact of a second dose of the ZV was of interest not only in terms of safety but also because a second ZV dose might have enhanced the immunogenic response over and above that provoked by the currently recommended single dose. ☐

UPCOMING EVENTS

4th Annual Canadian Centre for Vaccinology Symposium
April 23-24, 2012 / Halifax, Nova Scotia
http://www.centerforvaccinology.ca/continuing-education.html

AMMI-Canada/CACMID Annual Conference
May 3-5, 2012 / Vancouver, British Columbia
www.cacmid.ca/

30th Annual Meeting of the European Society for Paediatric Infectious Diseases
May 8-12, 2012 / Thessaloniki, Greece
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