April–June 2010

VACCINE RESOURCE LINE

A QUARTERLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

NACI recommendations for herpes zoster vaccination

Canada Communicable Disease Report (CCDR). *Online publication January 2010;36(ACS-1):1-19.*

The National Advisory Committee on Immunization (NACI) has now recommended the herpes zoster (HZ) vaccine for the prevention of HZ and its complications in individuals ≥60 years of age, citing good evidence for its efficacy and safety from the pivotal Shingles Prevention Study (SPS).

Highlights of other recommendations include:

- There is no recommendation for immunization in individuals with a past episode of HZ, even though patients who have had a previous episode are at risk for further episodes. This is because patients with a prior history of HZ were excluded from the SPS and therefore the efficacy of the vaccine could not be demonstrated in this population.
- The vaccine should be given to patients irrespective of a prior history of chickenpox or documented varicella infection. As NACI pointed out, nearly all Canadians will have been exposed to chickenpox even if they cannot recall being diagnosed with varicella and there is no known safety risk associated with vaccination of healthy individuals.
- Booster doses of the vaccine are not recommended for healthy individuals. Protection against HZ infection has not been assessed beyond four years and it is not yet known whether booster doses of the vaccine will be beneficial.
- Individuals who inadvertently receive systemic antiviral therapy active against varicella within two days before and 14 days after receiving the vaccine may benefit from a second dose of the vaccine 42 days or later and after discontinuing antiviral therapy.
- The vaccine may also be used in patients aged ≥50 years. As NACI noted, the HZ vaccine has been shown to be safe and immunogenic in this patient group but its effectiveness has only been studied in those aged ≥60 years and the greatest benefit can be expected in this age group. It is also uncertain whether vaccination given to individuals <60 years will provide ongoing protection as patients age when the incidence of HZ is highest.
- The trivalent influenza vaccine may be given concomitantly with the HZ vaccine at a different body injection site, but the 23-valent pneumococcal polysaccharide vaccine and the HZ vaccine should be given at least four weeks apart.

FEATURING SELECTED SUMMARIES FROM:

Canada Communicable Disease Report: *www.phac-aspc.gc.ca/naci-ccni/index-eng.php*

Vaccine: *www.sciencedirect.com/science journal/0264410X*

J Natl Cancer Inst: *www.jnci.oxfordjournals.org*

J Infect Dis: *www.journals.uchicago.edu/toc/jid/current*

Decline in varicella hospitalization rates after widespread vaccine uptake in Australia

Carville et al. A decline in varicella but an uncertain impact on zoster following varicella vaccination in Victoria, Australia. Vaccine *2010;28(13):2532-8.*

A significant decline in the varicella hospitalization rate, mainly in the target vaccine age group of children under the age of 5 years, has been documented following the introduction of the varicella vaccine in Victoria, Australia. In contrast, there has been a steady increase in hospitalization rates for HZ that correspond to the introduction of the varicella vaccine, Australian researchers reported.

Dr. Kylie Carville, University of Melbourne, Australia, and colleagues extracted data associated with any diagnosis of varicella or HZ from the Victoria Admitted Episodes Dataset from 1995 to 2007. The dataset revealed that there were 3853 admissions to Victoria hospitals for varicella between 1995 and 2007, 64% of them having varicella as the principal diagnosis. "Varicella hospitalizations increased in Victoria from 1995 to 2000 and subsequently declined," investigators added, "and over the complete period in which vaccine was available [privately or publicly, from 2000 to 2007], all admissions with varicella decreased 7% per year."

Among children under the age of 5, admissions for varicella declined by 9% from 2000 to 2005 and continued to decline in 2006-2007, they added. Declines in all varicella admissions were seen between 2000 and 2005 for other age groups, including children between the ages of 5 and 9 years, and those from 10 to 19 years old. Interestingly, there was a 39% decrease in varicella admissions in adults between the ages of 20 and 49 years in 2006-2007. Overall, between 2000 and 2007, varicella hospitalizations in Victoria declined by 44%, researchers observed. For HZ, a total of 10,535 admissions

to Victoria hospitals were documented between 1995 and 2007, 45% of them being for HZ as the principal diagnosis. "Admissions declined in the period in which no [varicella] vaccine was available but increased during the period of private vaccine availability, with a further increase in the mean rate of hospitalization in 2006-2007," investigators noted.

Overall, trends in HZ hospitalization were influenced largely by those ≥80 years of age. Between 1995 and 1998, the HZ hospitalization rate decreased by 13% per year but increased by 5% per year between 1998 and 2007 in this age group. The authors cautioned that due to the nature of their study, they were unable to determine why HZ hospitalizations have increased. Nevertheless, regardless of cause, "There has been an increase in both serious HZ requiring hospitalization and HZ in the community that is sufficiently worrying to occasion an out-of-hours medical consultation. The HZ vaccine, where not funded, should be considered for inclusion in publicly-funded adult vaccination programs," they summarized.

Ongoing HPV vaccination will result in notable reductions in all HPV-related disease end points

Muñoz et al. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. J Natl Cancer Inst *2010;102(5):1-15.*

According to FUTURE study investigators, ongoing vaccination programs against human papillomavirus (HPV) infection in adolescent girls and young women will result in notable reductions in all HPV-related disease in both the short and longer term.

Dr. Nubia Muñoz, Lyon, France, and multicentre colleagues assessed the impact of the quadrivalent vaccine on all HPV-associated genital disease in a population that approximates sexually-naive women who were negative to 14 HPV types at baseline as well as in a mixed population of HPV-exposed and unexposed women (intention-to-treat [ITT] group).

At an average follow-up of 3.6 years (maximum 4.9 years), vaccination was up to 100% effective against the risk of HPV 16- and 18-related high-grade cervical, vulvar and vaginal lesions as well as HPV 6- and 11-related genital warts in the sexually-naive cohort. Efficacy was lower in the ITT group but the vaccine still significantly reduced the risk of any high-grade cervical lesions by 19%, vulvar and vaginal lesions by 50.7% and genital warts by 62% relative to placebo.

In the same sexually-naive cohort, prophylactic vaccination also reduced HPV 16-related Pap test abnormalities by 92% and HPV18-related Pap test abnormalities by 97%. "The impact on Pap test abnormalities irrespective of causal HPV type as expected was less, with an overall reduction of 17.1%," researchers noted. In the same cohort, vaccination against HPV infection also significantly reduced the risk of colposcopy by 19.8%, any cervical biopsy by 22% and any cervical definitive therapy by 42.3%. There was also a 43.3% reduction in all procedures for external genital lesions. Reductions in the same end points were again lower in the ITT group but remained significant at 11.3% for all categories of Pap test diagnoses, 23% for cervical definitive therapy and 28.3% for procedures for external genital lesions.

"High-coverage HPV vaccination programs among adolescents and young women may result in a rapid reduction of genital warts, cervical cytological abnormalities and diagnostic and therapeutic procedures and, in the longer term, substantial reductions in the rates of cervical, vulvar and vaginal cancers may follow," investigators concluded.

Anamnestic responses better in adolescents boosted with adult dose of the hepatitis B vaccine

Chaves et al. Improved anamnestic response among adolescents boosted with a higher dose of the hepatitis B vaccine. Vaccine *2010;28(16):2860-4.*

According to results from the first study of its kind, anamnestic responses in adolescents who are boosted with a higher dose of the hepatitis B vaccine are significantly better than when boosted with a pediatric dose but it is still not optimal.

Dr. Sandra Chaves, Centers for Disease Control and Prevention, Atlanta, Georgia, and multicentre colleagues boosted a group of adolescents with an adult dose of the hepatitis B vaccine and compared their anamnestic response to that of adolescents boosted with a pediatric dose of the same vaccine. "From a total of 158 eligible participants, 89 adolescents were enrolled in the adult booster-dose comparison study group," the authors noted. The median age in the pediatric booster-dose group was 15.7 years vs. 17.7 years for the adult booster study group.

Among adolescents who had lost protective antibody levels against hepatitis B, a higher proportion (60%) had an anamnestic response when boosted with the adult dose compared with 43.8% for adolescents boosted with the pediatric dose, investigators reported. Conversely, 35% of adolescents still had anti-HB titres below protection levels following the adult booster dose compared with 52% of those who received the pediatric booster dose.

"This is the first study to investigate whether the capacity to generate an adequate anamnestic response among those vaccinated starting at birth is associated with the antigen concentration used for the booster dose given," investigators observed. "A higher hepatitis B antigen concentration might be needed to trigger an optimal immune memory response long after anti-HBs titres become undetectable."

Widespread vaccination against rotavirus infection could substantially reduce overall burden of disease in England and Wales

Atchison et al. Modelling the seasonality of rotavirus disease and the impact of vaccination in England and Wales. Vaccine *2010;28(18):3118-26.*

Widespread vaccination against rotavirus (RV) infection in England and Wales could reduce the overall burden of disease by 61% if coverage levels achieved are comparable to levels achieved with other childhood vaccines, according to predictions made by UK researchers.

Christina Atchison, London School of Hygiene and Tropical Medicine, UK, and colleagues developed a dynamic model of RV transmission and applied it to daily case reports of RV disease from England and Wales. They then used this model to examine the potential epidemiological impact of an RV mass vaccination program in the two countries. "We initially investigated the effects of a two-dose [monovalent] RV mass vaccination programme with doses given at two and four months of age," researchers noted. They also assumed that the full vaccine course would confer a protective effect against infection and disease similar to that of a primary natural infection. Researchers also assumed that 96% of recipients of the full two-dose regimen would be successfully immunized to a natural primary RV infection. At the same time, they explored a variety of vaccine

coverage levels and determined the long-term relative effects of both direct and indirect protection.

As researchers determined, vaccination would result in an increasing decline in the numbers of infections as well as a delay in the start of the RV season in the first and second post-vaccination years. For example, in an average pre-vaccination season, peak activity would be seen in early March. In the second year post-vaccination, peak activity would be seen in April. "With 91% coverage levels for the full two-dose schedule, the model predicts a 72% reduction in the seasonal peak in incidence," they observed. Researchers also predicted that the seasonal pattern of RV disease would stabilize approximately 10 years after introduction of the vaccine and that the average age of children who do become ill would increase from 1.4 years pre-vaccination to 5.3 years post-vaccination. The model also predicted that with 91% coverage, an additional 3% reduction in the number of reported cases could be expected from indirect effects of the vaccine.

"The model predicts that a single-, two- or three-dose course of [pentavalent] RV vaccine will not eliminate RV disease completely if the effect of the vaccine is truly comparable to the protection provided by natural infection [but] vaccination effects predicted are in keeping with those observed in the US. This dramatic fall in disease incidence would more than likely result in a fall in burden on health care services attributable to RV gastroenteritis," they reported.

Primary and revaccination with the PN23 vaccine induces persistent antibody response out to five years

Musher et al. Safety and antibody response, including antibody persistence for 5 years, after primary vaccination or revaccination with pneumococcal polysaccharide vaccine in middle-aged and older adults. J Infect Dis *2010;201(4):516-24.*

Primary vaccination with the 23-valent pneumococcal polysaccharide vaccine (PN23) and revaccination with the same vaccine induce antibody responses that persist over five years in vaccine recipients ≥50 years of age.

Dr. Daniel Musher, Michael E. DeBakey VA Medical Center, Houston, Texas, and multicentre colleagues assessed antibody levels for five years following primary vaccination or revaccination with the PN23 vaccine in individuals between the ages of 50 to 64 and those ≥65 years with a past history of PN23 vaccination three years or more prior to study entry or no prior vaccination. "Revaccination subjects who were 50 to 64 years old must have received their primary vaccination ≥3 years previously, whereas revaccination subjects who were ≥65 years old needed to have received their primary vaccination between 3 and 5 years previously," investigators explained.

A total of 1008 subjects were enrolled in the study in 1997 and 1998 and received a dose of the PN23 vaccine or placebo; of these, 551 completed year 5. For each revaccination group, the median time since primary vaccination was 3.9 years. "After primary vaccination or revaccination with PN23, levels of IgG to all eight serotypes increased significantly from baseline to day 30 in all four subject groups," investigators reported.

Antibody levels on day 30 were marginally higher for the primary vaccination groups than for the revaccination groups, they added, but the differences were still significant. IgG geometric mean concentrations also increased from day 30 to day 60 for the older primary vaccination group, the older revaccination group and the younger revaccination group. Most vaccines had some local adverse experiences at the injection site, although they were less common in the older age group receiving PN23 for the first time and more common in those who were being revaccinated.

"Antibody levels appeared to peak at 30 to 60 days… and then subsided over the ensuing one to two years to a plateau that remained about twofold higher than the mean baseline levels for vaccine-naive subjects," investigators observed. " [Findings] support the current ACIP recommendations which state that PN23 should be administered to all persons ≥65 years old, even if they have been vaccinated previously."

Most emergency and internal medicine physicians immunized against influenza in 2008-2009

deSante et al. Physician attitudes towards influenza immunization and vaccine mandates. Vaccine *2010;28(13):2517-21.*

A survey of emergency medicine (EM) and internal medicine (IM) physicians at two tertiary care centres in the US showed the vast majority of them had been immunized against influenza in the 2008-2009 influenza season. There was also strong support in favour of mandatory immunization of all health care workers (HCWs).

Dr. Jennifer E. deSante, University of Pennsylvania School of Medicine, Philadelphia, and colleagues sent an anonymous electronic survey to house officers and attending physicians in the EM and IM departments at two tertiary care hospitals in the University of Pennsylvania Health Systems. "These departments were chosen because these specialists are most likely to provide initial care for patients with influenza-like illnesses," investigators noted, "and our primary outcome was physician opinions regarding mandatory immunization for HCWs."

Of the 221 physicians who completed the survey, 94% of respondents reported receiving the influenza vaccine during the 2008-2009 season. "Reasons most frequently given for vaccination were protection of themselves, their patients and their families," the authors observed, "and frequent patient contact was a strong predictor of immunization." At the same time, the surveyed physicians also demonstrated significant support for mandatory influenza vaccination, with 85% of respondents agreeing that vaccination should be mandatory for all HCWs. "That number rose to 90% when asked if all HCWs have an obligation to be vaccinated for the sake of their patients," researchers added. However, internal medicine physicians were significantly more supportive of mandatory immunization than emergency physicians, most likely a reflection of a difference in opinion regarding mandates between the two specialities. "As we hypothesized, physicians with more clinical exposure and those who cited patient safety as a reason were more likely to be vaccinated," the authors observed.

In contrast, hospital-based documentation at the study hospitals confirmed vaccination for only 60% of all HCWs and only 40% of house attendants during the same season. As study authors speculated, this is likely an under-representation of vaccination rates as it does not count all those vaccinated outside the hospital.

"Any unimmunized HCW has the potential to transmit influenza to a patient," investigators noted. "That the study hospitals have been strongly advocating influenza immunization for several years makes this ongoing risk of transmission more concerning and begs the question of whether non-mandated immunization programs can achieve their goals."

PPV-23 vaccine at 12 months following PCV-7 in infancy induces excellent booster responses

Russell et al. Safety and immunogenicity of the 23-valent pneumococcal polysaccharide vaccine at 12 months of age, following one, two, or three doses of the 7-valent pneumococcal conjugate vaccine in infancy. Vaccine *2010;28(18):3086-94.*

A booster dose of the 23-valent pneumococcal polysaccharide (PPV-23) vaccine given at 12 months of age following one, two or three doses of the 7-valent pneumococcal conjugate vaccine (PCV-7) in infancy induces an excellent booster response against all PCV-7 serotypes as well as significant responses against non-PCV-7 serotypes for up to five months following the booster dose.

Dr. Fiona M. Russell, University of Melbourne, Victoria, Australia, and multicentre colleagues carried out a phase II vaccine trial in Fiji to determine the safety, immunogenicity and impact on pneumococcal carriage of various vaccination regimens consisting of one, two or three doses of PCV-7 in infancy. The additional benefit of giving a booster dose of the PPV-23 vaccine at 12 months was also assessed.

A total of 552 infants were enrolled in the study, and the 12-month PPV-23 vaccine was given to 245 of them. "Two weeks following the PPV-23, geometric mean serotype-specific IgG antibody concentrations [GMCs] were significantly higher for all PCV-7 serotypes for children who had received either one, two or three PCV-7 doses in the primary series compared to levels prior to receiving the PPV-23 vaccine [each $P<0.001$]," investigators reported. For four of seven serotypes (4, 9V, 18C and 19F), the response was most profound in infants who received a single PCV-7 dose.

GMCs were also significantly higher two weeks following receipt of the PPV-23 booster dose compared with pre-PPV-23 levels for all PCV-7 serotypes in infants who had not received the PCV-7 vaccine in infancy ($P<0.001$). At 17 months, infants who had received the booster dose of the PPV-23 vaccine at 12 months continued to have significantly higher GMCs for all PCV-7 serotypes compared to infants who had not received the 12-month PPV-23 booster, although they had received the same number of doses of the PCV-7 vaccine (each $P<0.001$). "The single-PCV-7-dose group who received the PPV-23 [booster dose] continued to have higher GMCs compared to the two- or three-dose PCV-7 groups that did or did not receive the PPV-23 [booster dose]," investigators stated.

Assessing immunogenicity to non-PCV-7 serotypes, investigators also noted that GMCs and the proportion of infants with antibody concentrations ≥0.35 and ≥1 µg/mL were all significantly higher than pre-PPV-23 levels two weeks after receipt of the booster dose (each $P<0.001$). By 17 months of age, GMCs as well as the proportion of infants with antibody concentrations of ≥35 µg/mL were still significantly higher for all non-PCV-7 serotypes in infants who had received the PPV-23 vaccine at 12 months vs. those who had not (each $P<0.001$).

Low-grade fever following receipt of the PPV-23 booster at 12 months was common, occurring in 28.2% of the cohort while high-grade fever occurred in 6.1% of the cohort. However, local injection site reactions occurred in only a minority of recipients and all events resolved within 48 hours.

Investigators suggested that the better booster responses seen after only a single dose of the PCV-7 vaccine may be explained by the fact that a single antigen challenge may preferentially drive the induction of memory B-cells which are required for a booster response. Having a greater pool of memory B-cells would subsequently elicit a greater booster response, they added. □

UPCOMING EVENTS

Pediatric Academic Societies Annual Meeting
May 1-4, 2010 / Vancouver, British Columbia
www.pas-meeting.org

28th Annual Meeting of the European Society for Paediatric Infectious Diseases
May 4-8, 2010 / Nice, France
http://www2.kenes.com/espid2010/Pages/Home.aspx

Primary Care Today
May 6-8, 2010 / Toronto, Ontario
www.primarycaretoday.ca

26th International Papillomavirus Conference & Clinical and Public Health Workshops
July 3-8, 2010 / Montreal, Quebec
www.hpv2010.org

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