January-February 2008

VACCINE RESOURCE LINE

A MONTHLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

Updated NACI recommendations: infants and families likely to benefit from the pentavalent rotavirus vaccine

Canada Communicable Disease Report (CDDR). *Online publication 22 January 2008;34(ACS-1):1-33.*

The National Advisory Committee on Immunization (NACI) has concluded that based on the epidemiology of rotavirus (RV) infection in Canada, infants and their families would likely benefit from the currently approved pentavalent RV vaccine as widespread uptake would substantially reduce morbidity and care-related costs due to RV infection.

Almost all children experience an episode of RV gastroenteritis by five years of age and RV causes the majority of gastroenteritis episodes in children requiring hospitalization. In Canada, NACI estimates these rates range from one in 62 to one in 312 children under the age of five. Even among children who do not require hospitalization, the annual health care burden attributable to RV infection here in Canada is high, accounting for some 41,000 physician consultations and 17,000 emergency room visits each year.

Based on three separate clinical trials in which half of almost 72,000 infants received the pentavalent vaccine, the triple-dose schedule prevented over 98% of all severe RV gastroenteritis caused by the four G serotypes in the vaccine and over 73% of RV gastroenteritis of any severity. It was also 74% effective against RV caused by non-vaccine serotype G9. The largest of these studies, the REST (Rotavirus Efficacy and Safety Trial), also showed that the vaccine reduced G1-G4 RV-associated hospitalizations or emergency room visits by 94.5% and non-urgent office or clinic visits by 86%. Among parents or guardians of over 68,000 infants studied, the vaccine also reduced the number of workdays lost because of RV infection by over 86%.

Based on the Rotavirus Gastroenteritis Cohort Model—and assuming that approximately 94% of RV disease in Canada is caused by the strains contained in the vaccine—NACI calculated that implementation of universal immunization of all Canadian infants could prevent as many as 56,000 cases of gastroenteritis, 33,000 physician visits, 15,000 emergency department visits and 5000 hospitalizations a year.

Out of almost 72,000 infants involved in the clinical trials program, only six cases of intussusception were documented following receipt of the vaccine vs. five in the placebo group and there has been no evidence of clustering of cases within the first few weeks after infants received the vaccine, when the risk of intussusception is highest.

NACI recently issued the following recommendations on the use of the pentavalent RV vaccine in Canada:

- Infants should receive the first dose of the vaccine between the ages of six and 12 weeks.
- The first dose should not be given after 12 weeks of age (i.e. 13 weeks minus a day).
- Following the initial dose, subsequent doses should be administered at an interval of four to 10 weeks between each dose.
- All three doses, given orally, should be completed before infants reach 32 weeks of age.
- Infants should receive each dose either at a clinic or office setting under the direction of a health care provider.
- If an infant spits up or regurgitates the vaccine, a replacement dose is not recommended.
- If the first dose of the vaccine is inadvertently given off-label at 13 weeks of age and older, the rest of the vaccination series should be completed with a minimum of four weeks between each dose.
- Infants who have had an episode of RV gastroenteritis before receiving the full vaccination should still receive the three-dose schedule as the initial infection often provides only partial immunity.
- Breastfed infants can also receive the vaccine.

CPS endorses routine HPV vaccination in girls

Infectious Diseases and Immunization Committee, Canadian Paediatric Society (CPS). Paediatrics & Child Health *2007;12(7):599-603.*

The Canadian Pediatric Society (CPS) has endorsed routine administration of the human papillomavirus (HPV) vaccine to all girls between the ages of 9 and 13 years, as early as programmatic issues allow.

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In a review of the safety and efficacy of the HPV vaccine, the CPS emphasized the need to give the vaccine before girls acquire the infection. Since infection can occur with sexual touching and not just with intercourse, it is of interest that approximately 1% to 4% of Canadian children have had intercourse by grade 6; 3% to 4% by grade 7; 17% to 23% by grade 9; and 40% to 46% by grade 11 or by 16 years of age. "Sexual touching estimates are likely higher given that sexual touching and exploration often precede intercourse by some time," they noted.

The CPS also made the following recommendations:

- Specific attention should be paid to the immunization of street-involved girls and youth, as well as those taken into foster care or group homes, where there is a higher risk of early-onset sexual activity.
- The vaccine should be given to all unimmunized girls ≥13 years of age as part of a "catch-up" program.
- Females who have had a previous Pap abnormality, genital warts or known HPV infection should still be offered the vaccine because they are unlikely to have been infected with all four HPV types included in the vaccine and thus may still benefit from it.
- Physicians must still counsel immunized females to take part in cervical cancer screening programs once they become sexually active.
- All children and adolescents who are sexually active should be educated on behaviours that can reduce acquisition of nonvaccine HPV types and other sexually-transmitted infections including consistent condom use, regardless of their immunization status. The CPS, however, does acknowledge that consistent condom use is not completely effective against HPV infection.
- Immunocompromised individuals may be offered the vaccine at the same doses and schedule, based on expert opinion.
- Studies evaluating the efficacy of the vaccine in boys should be earmarked as an urgent research priority as immunological data in boys to date are convincing.

Genital warts diagnosed in one of 10 Nordic women

Kjaer et al. The burden of genital warts: a study of nearly 70,000 women from the general female population in the 4 Nordic countries. J Infect Dis *2007;196(10):1447-54.*

One in 10 Nordic women experience the medical and psychosocial burden associated with genital warts, according to the largest study to date assessing their prevalence. The incidence is also increasing among younger birth cohorts.

Prof. Susanne Kruger Kjaer, Danish Cancer Society, Copenhagen, and multicentre colleagues assessed the occurrence and correlates of genital warts in a random sample of 69,147 women between the ages of 18 and 45 living in Denmark, Iceland, Norway and Sweden. "The majority of the women were married or cohabiting [69.6%]," the authors noted, "[while] the median lifetime number of sex partners was five and the median age at first intercourse was 16 years."

A total of 7351 (10.6%) of the entire cohort reported having had at least one previous episode of clinically diagnosed genital warts, at a mean age of approximately 22 years across all four countries. The prevalence of ever having had genital warts ranged from 12% in Iceland to 9.5% in Norway. "For Iceland, Norway and Sweden, the prevalence initially increased with increasing birth cohort," investigators observed, while for older birth cohorts, there was a lower prevalence. In contrast, investigators observed a continuously increasing prevalence of genital warts with increasingly older birth cohorts among Danish women.

Investigators also observed a tendency—most pronounced in Iceland—for younger birth cohorts to have more sexual partners than older cohorts, except among women in the youngest birth cohort who were too young to have accumulated many partners. Indeed, the most important factor seen in association with clinically diagnosed genital warts was the lifetime number of sexual partners, the odds ratio for those who reported 15 or more partners being 9.45 compared with those who reported having only one partner. The use of oral contraceptives, condom use, ever having had an abortion, more education and a history of smoking for more than 59 pack-years also increased the likelihood that women would report an episode of genital warts.

"Consistent with other studies… we observed that a history of genital warts correlated strongly with indicators of sexual habits, such as lifetime number of sex partners and previous sexually-transmitted infections… with 82% of all cases occurring in women with five or more partners," investigators reported. "In addition, the results of this study indicate an increasing incidence of genital warts among younger birth cohorts."

Given these findings, investigators felt that their observations "will fill a gap that is necessary for understanding the changing dynamics of genital warts in the population, for generating estimates of the economic burden of HPV in relation to genital warts and for developing mathematical models to project the long-term benefits and costs of HPV vaccination."

Majority of Canadian parents would have their daughters vaccinated against HPV

Ogilvie et al. Parental intention to have daughters receive the human papillomavirus vaccine. CMAJ *2007;177(12):1506-12.*
Duval et al. Vaccination against human papillomavirus: a baseline survey of Canadian clinicians' knowledge, attitudes and beliefs. Vaccine *2007;25(45):7841-7.*

The majority of parents recently surveyed across Canada would have their daughters vaccinated against the human papillomavirus (HPV), at least in the context of a publicly-funded, school-based program offered in grade 6.

Dr. Gina Ogilvie, University of British Columbia, Vancouver, and multicentre colleagues collected answers from 1350 respondents with female children as to their intention to have their daughters vaccinated against HPV. The team also looked at factors that might predict whether parents intended to have their daughters vaccinated. Interestingly, only about half of the respondents had heard of HPV and only about one-quarter knew that HPV is transmitted through sexual contact.

Of this group of 1350 respondents, 73.8% indicated that they intended to have their daughters vaccinated against HPV. "In different regions of the country, the intention to vaccinate varied, from a low of 62.8%... in British Columbia and the Yukon Territory to a high of 82.6%… in Atlantic Canada," investigators commented. Somewhat surprisingly, neither cultural background, education nor religious beliefs were associated with parental intention to vaccinate their daughters.

In contrast, results from multivariate analyses showed that parents who had a positive attitude towards vaccines in general—and the HPV vaccine in particular—as well as those who felt that the vaccine would have a limited influence on their daughter's sexual behaviour, were more likely to indicate that they would have their daughters vaccinated against HPV. Parents were also more amenable if they believed that someone they knew would get cervical cancer. Recommendations in favour of HPV vaccination from different groups, including health care professionals (and physicians in particular), also significantly influenced parental decision to vaccinate, according to survey findings.

A different survey of Canadian obstetrician/gynecologists', family doctors' and pediatricians' knowledge, attitudes and beliefs about HPV infection and prevention also showed very high support for the vaccine.

Based on results from an anonymous questionnaire mailed to 2500 physicians—about half of whom responded—95% of respondents felt that the vaccine should be given to girls prior to

their sexual debut. Eighty-eight per cent of respondents intended to recommended the vaccine if publicly funded, but only slightly fewer respondents (84%) also intended to recommend vaccine if patients had to pay for the vaccine themselves. Some 94% of respondents also intended to recommend a vaccine that would protect against both cervical cancer and genital warts, while 89% of respondents indicated they would recommend a vaccine that protects against cervical cancer alone.

"Overall, more than two-thirds of physicians expect important benefits from HPV vaccination," the authors noted, "[and] although knowledge about HPV and its prevention was generally poor, virtually all clinicians surveyed are supportive of HPV vaccination and feel that it should be given to girls before the onset of sexual activity."

New vaccines found to be highly cost-effective

Pellissier et al. Evaluation of the cost-effectiveness in the United States of a vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. Vaccine *2007;25(49):8326-37.*
Newall et al. The cost-effectiveness of rotavirus vaccination in Australia. Vaccine *2007;25(52):8851-60.*

Two separate studies analyzing the cost-effectiveness of two new vaccines, one for older adults and one for infants, have both found the new vaccines would be highly cost-effective when administered to the target age groups.

Dr. James Pellissier, Blue Bell, Pennsylvania, and multicentre colleagues developed an age-specific decision analytic model to estimate the lifetime costs and outcomes associated with herpes zoster (HZ), postherpetic neuralgia (PHN) and other zoster-related complications for individuals ≥60 years of age who received the vaccine vs. those who did not. Calculations used in the model were based on clinical trial evidence in which clinically meaningful reductions in the incidence of both viral infections vs. placebo were demonstrated.

"For a representative cohort of 1 million US vaccine recipients aged ≥60 years, use of the zoster vaccine was projected to eliminate 75,548 to 88,928 HZ cases and over 20,000 PHN cases," the authors reported. In addition, over 300,000 outpatient visits, 375,000 prescriptions, 9700 emergency room visits and 10,000 hospitalizations would also be eliminated by uptake of the vaccine in the target age group. This would translate into savings of between $82 to $103 million in health care costs associated with the diagnosis and treatment of HZ, PHN and other zoster-related complications, researchers added.

In terms of cost per quality-adjusted life-year (QALY) gained—the main outcome measure of the analysis—researchers also calculated that the cost-effectiveness ratio would range from a low of $16,229 to a high of $27,609 per QALY gained, a finding that prompted investigators to conclude that the zoster vaccine—at a price of US$150—is likely to be cost-effective for immunocompetent adults ≥60 years of age, using commonly cited thresholds for judging cost-effectiveness. They also noted that the cost-effectiveness of the zoster vaccine is comparable to that for other adult preventive measures.

In a separate study, Dr. Anthony Newall, University of Sydney, Australia, and multicentre colleagues determined the cost-effectiveness of two rotavirus vaccines administered in Australia. Researchers modelled specific outcomes of disease, including hospitalizations, emergency department visits, general practitioner visits and deaths that the vaccines would attenuate or eliminate if used as recommended. The model followed a hypothetical cohort of children over the first five years of life because the majority of the disease burden from rotavirus occurs under five years of age.

Given as recommended either in a two- (Rotarix) or three-dose (RotaTeq) schedule in infancy, both vaccines resulted in additional QALYs, at a cost of $60,073/QALY with the former and $67,681/QALY with the latter. Universal vaccination with either vaccine also would result in very comparable reductions in death, hospitalizations, emergency department visits and general practitioner visits due to rotavirus infection in the modelled age cohort.

"Rotavirus-associated mortality in Australia is modest in comparison to that found in the developing world," the authors noted, "[but] disease morbidity is significant and is associated with considerable health care utilization. The results of this cost-effectiveness analysis suggest that rotavirus vaccination could be cost-effective dependent on vaccine price."

Immunogenicity of aerosolized measles vaccine

Low et al. Immunogenicity and safety of aerosolized measles vaccine: Systematic review and meta-analysis.
Vaccine *2008;26(3):383-98.*

Aerosolized measles vaccine appears to be equally or even more immunogenic than subcutaneous (s.c.) measles vaccine in children ≥10 months of age, according to a systematic review of the literature.

Dr. Nicola Low, University of Bern, Switzerland, and colleagues conducted a systematic review and meta-analysis of published studies to determine the immunogenicity and safety of the aerosolized measles vaccine delivery in children of different ages and in adults. Seven randomized trials were included in their analysis, as were four non-randomized trials and six uncontrolled studies. In total, investigators obtained serological outcome data on 2887 vaccine recipients.

In children <10 months old, studies were heterogeneous. In four comparative studies, for example, seroconversion rates with the aerosolized vaccine were lower than they were with the s.c. formulation and in two of these four studies, "the difference was unlikely to be due to chance," they observed.

However, in children between the ages of 10 and 36 months, the pooled seroconversion rate following aerosolized vaccine delivery was 93.5% vs. 97.1% following the s.c. vaccine. In older children between the ages of 5 and 15, studies were again heterogeneous, but in all comparative studies, the aerosolized vaccine was more immunogenic. Adverse events following aerosolized vaccine delivery were generally mild and infrequent, they also noted. The s.c. measles vaccine has been available for more than 40 years but as late as 2004, there were still 10 countries where more than half of one-year-olds had not received a single dose of the measles vaccine.

"Aerosols delivered to the respiratory mucosa are the natural route of transmission for measles virus and the most promising non-injectable method of vaccination studies so far," investigators observed, "and simplifying the delivery of measles vaccine could increase the coverage, acceptance, safety and efficacy of measles elimination efforts."

Invasive pneumococcal disease due to non-PCV7 serotypes increasing in Spain

Muñoz-Almagro et al. Emergence of invasive pneumococcal disease caused by nonvaccine serotypes in the era of the 7-valent conjugate vaccine. Clin Infect Dis *2008;46(2):174-82.*

A significant increase in invasive pneumococcal disease in the era of the 7-valent conjugate vaccine has been seen in Barcelona, Spain, most of it caused by virulent clones of non-PCV7 serotypes.

Dr. Carmen Muñoz-Almagro, *Hospital Universitari Sant Joan de Deu*, Barcelona, and colleagues from other area centres carried out a 10-year prospective study of all children with culture-proven invasive pneumococcal disease (IPD) admitted to the Sant Joan de Deu Hospital. The PCV7 vaccine was introduced in Spain in June 2001 and the current estimate of PCV7 coverage is between 45% and 50%.

Investigators compared the rates of IPD recorded in the prevaccine era between 1997 and 2001 with rates in the vaccine period between 2002 and 2006. In children under the age of two years, the rate of IPD rose from 32.4 episodes per 100,000 in the prevaccine era to 51.3 episodes per 100,000 in the vaccine era (a 58% increase). In children between the ages of two and four years, the rate increased from 11.3 episodes per 100,000 in the prevaccine interlude to 26.5 episodes per 100,000 in the vaccine interlude (an increase of 135%). "At clinical presentation, the rate of pneumonia and/or empyema among children aged <5 years increased from 3.6 episodes per 100,000 population to 15.1 episodes per 100,000 population," they added—a 320% increase between the two comparative intervals.

As they also noted, the increased rates of IPD seen in all age groups in the vaccine era were mainly caused by non-PCV7 serotypes. For example, in the prevaccine era, IPD caused by non-PCV7 serotypes represented only 38% of all IPD compared with 72% of all IPD in the vaccine era. The increased rate of IPD caused by non-PCV7 serotypes was also associated with changes in clinical presentation, overgrowth of previously established virulent clones of non-PCV7 serotypes and capsular switching among vaccine and nonvaccine serotypes. As has been seen elsewhere, the group observed a "substantial reduction" in the rate of antibiotic-resistant strains causing IPD after the PCV7 vaccine was introduced because antibiotic resistance is mainly associated with PCV7 serotypes.

Investigators cautioned that the results of their study must be considered preliminary because of the low vaccine coverage rate in their area and because other factors might have contributed to the observed epidemiological changes. Nonetheless, they still concluded that since the introduction of the PCV7 for children, "there has been an emergence of IPD caused by virulent clones of non-PCV7 serotypes."

Modern cell culture vaccines recommended for all at risk for rabies exposure

Leung et al. Rabies: Epidemiology, pathogenesis, and prophylaxis. Adv Ther *2007;24(6):1340-7.*

Individuals who are most likely to be exposed to rabies, including veterinarians, animal handlers and rabies research personnel, should receive modern cell culture vaccines to prevent infection. The same recommendation can be considered for all travelers to countries where the risk for rabies exposure is high or who are travelling to countries where immediate access to appropriate medical care is limited.

Dr. Alexander Leung, University of Calgary, Alberta, and multicentre colleagues reminded readers that rabies is "invariably fatal" once symptoms develop. "Because rabies is untreatable, prevention is of utmost importance," they stated. The standard pre-exposure regimen consists of three doses of 1 mL of modern cell culture vaccine on days 0, 7, and 21 or 28. "The vaccine should be given intramuscularly (i.m.) in the deltoid muscle of adults and in the anterolateral aspect of the thigh of infants because administration in the adipose tissue might result in lower antibody titres," researchers explained.

Administered as recommended, the seroconversion rate is approximately 98% after primary vaccination, although a booster dose is recommended for high-risk individuals if antibody titres fall below acceptable levels. Between 30% and 50% of those who are bitten by a known rabid animal and who have not received post-exposure prophylaxis develop rabies. Key to post-exposure prophylaxis is wound care. "Wounds should be immediately washed with copious amounts of water and cleansed with soap," the authors advised, "and alcohol, cetrimide, quaternary ammonium compounds, iodine and povidone should be used if available." If avoidable, wounds should not be sutured, they added.

Notably, for individuals who have not received pre-exposure prophylaxis within the previous two years, human rabies immune globulin (HRIG) should be given within seven days of exposure to rabies at a dose of 20 IU/kg of body weight. HRIG provides immediate rabies-neutralizing antibodies for a short time before the body generates active antibodies to the vaccine.

Individuals who have not been previously vaccinated against rabies should also receive 1 mL of modern cell vaccine i.m. on days 0, 3, 7, 14 and 28, although 0.1 mL can be given intradermally at eight different sites on day 0, at four sites on day 7 and at one site on days 28 and 91. Those who have been previously vaccinated require only two i.m. doses of the vaccine on days 0 and 3. ❑

UPCOMING EVENTS

Infectious Diseases in Clinical Practice: Update on Inpatient and Outpatient Infectious Diseases
February 17-22, 2008 / Kauai, Hawaii

AMMI Canada-CACMID Annual Conference
February 27-March 3, 2008 / Vancouver, British Columbia

6th International Conference on Emerging Infectious Diseases (ICEID)
March 16-19, 2008 / Atlanta, Georgia

42nd National Immunization Conference
March 17-20, 2008 / Atlanta, Georgia

3rd International Conference on TB Vaccines for the World
April 9-11, 2008 / Atlanta, Georgia