October-December 2010

VACCINE RESOURCE LINE

A QUARTERLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

Broadening HPV vaccination to boys, men

Elbasha E, Dasbach E. Impact of vaccinating boys and men against HPV in the United States. Vaccine *2010;28:6858-67.*
Kim J. Targeted human papillomavirus vaccination of men who have sex with men in the USA: a cost-effectiveness modelling analysis. Lancet Infect Dis *2010;10:845-52.*
Oteng et al. Evaluating societal preferences for human papillomavirus vaccine and cervical smear test and screening programme. Sex Transm Infect *2010. Published online October 18, 2010.*

Broadening the current quadrivalent human papillomavirus (HPV) recommendation (already in effect for girls and women in the US) to include boys and men between the ages of 9 and 26 would provide substantial public health benefits and is cost-effective at commonly cited thresholds, according to an economic analysis.

Researchers Elamin Elbasha and Erik Dasbach, North Wales, Pennsylvania, assessed the public health impact and economic consequences of vaccinating American boys and men with the quadrivalent HPV vaccine by using mathematical population models accounting for direct and indirect protective effects of vaccination. Analyses showed that through indirect effects of vaccination, the incidence of genital warts among men fell following the introduction of a female-only vaccination program, but an additional reduction in the incidence of genital warts among men could be achieved by extending vaccination to males. "The direct and indirect effects of girls- and women-only vaccination on HPV-related diseases among women are substantial," they added.

The inclusion of boys and men in the vaccination program provided additional direct and indirect benefits by further reducing the prevalence of HPV infection in the population. For example, vaccination steadily reduced the incidence of HPV 6, 11, 16 and 18-related head and neck cancer among both men and women. The largest reduction was accomplished by vaccinating both sexes. As the authors explained, because HPV infection takes a long time to progress to cancer, the effect of vaccination on any reduction in the incidence of cancer and cancer deaths was more gradual in comparison with that of genital warts.

However, when measured in terms of cumulative cases prevented in the US population, "the public health impact of vaccinating boys and men is also substantial," they noted, decreasing the mean cumulative number of genital wart cases among women by 1,849,000; cervical intraepithelial neoplasia (CIN) 2/3 cases by 708,000; cancer cases by 45,000; and cancer deaths by 15,000 among women within 100 years of introducing the quadrivalent vaccine.

Among men, the mean cumulative number of genital wart cases would be reduced by 3,297,000; cancer cases by 71,000; and cancer deaths by 25,000 after 100 years of vaccination. "By including major HPV-related diseases in our models, we show that adding boys and men 9-26 years of age to the HPV vaccine program is also cost-effective at the commonly cited thresholds of $100,000/quality-adjusted life-year (QALY) and $50,000/QALY,"researchers stated, "and this conclusion is robust across all the simulations we performed."

Another cost-effectiveness modelling analysis carried out by Dr. Jane Kim, Harvard School of Public Health, Boston, Massachusetts, concurred: in a scenario of HPV vaccination of men who have sex with men at 12 years of age without prior exposure to HPV, vaccination cost $15,290/QALY gained compared with no vaccination. Vaccination of the same group at 20 or 26 years after exposure to HPV was less cost-effective but was still less than $50,000/QALY under most scenarios.

Bridgette Oteng, MSc, University of British Columbia, Vancouver, and colleagues surveyed about 1150 Canadians (mean age 44 years) for their preferences regarding HPV vaccination. Respondents indicated that they preferred a program that targeted both genders; a vaccine that gave protection from both genital warts and cervical cancer; and that they were willing to pay for the additional protection afforded by the quadrivalent over the bivalent vaccine.

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New quadrivalent vaccine against meningococcal disease proven noninferior to currently licensed quadrivalent vaccine for children 2-10 years of age

Halperin et al. Comparison of the safety and immunogenicity of an investigational and a licensed quadrivalent meningococcal conjugate vaccine in children 2-10 years of age. Vaccine *2010;28:7865-72.*

A new quadrivalent vaccine against meningococcal disease, MENACWY-CRM, has been proven to be noninferior to the currently licensed quadrivalent vaccine, MCV4, for all 4 serogroups in the vaccine, and it was statistically superior for

serogroups C, W-135 and Y, according to a recent comparison of the two vaccines in children between the ages of 2 and 10 years. The MENACWY-CRM vaccine is already licensed for use in individuals between the ages of 11 and 55.

Dr. Scott Halperin, Director, Canadian Center for Vaccinology, Dalhousie University, Halifax, and multicentre colleagues compared the safety and immunogenicity of MenACWY-CRM to the MCV4 vaccine, which is licensed in young children. A total of 2820 children between the ages of 2 and 10 received either vaccine. Children were stratified by age: the 2- to 5-year-olds (n=1700) received either 2 doses of MenACWY-CRM or one dose of either vaccine; children between the ages of 6 and 10 years (n=1120) received a single dose of either vaccine. Seroresponse was defined as a serum bactericidal assay using human complement (hSBA) of ≥8 in each of the 2 age groups 28 days after receiving a single dose of either vaccine.

At study end, MenACWY-CRM met statistical superiority criteria vs. MCV4 for serogroups W-135 and Y and was non-inferior for serogroup C in both age groups. For serogroup A, non-inferiority criteria were not met; the serogroup A seroresponse rates for MenACWY-CRM and MCV4, respectively, were 72% and 77% in 2- to 5-year-olds, and 77% and 83% in 6- to 10-year-olds. When the 2 age groups were combined (2- to 10-year-old children), MenACWY-CRM was non-inferior to MCV4 for all 4 serogroups, and statistically superior for serogroups C, W-135 and Y. Reactions to both vaccines were largely mild and self-limited.

As the authors noted, the relatively low incidence of meningococcal disease makes demonstration of efficacy of new vaccines impractical. "Instead, licensure of new products is based on demonstrating noninferiority in the immune response to the vaccine using immunological surrogates of protection." Although bactericidal activity at a serum dilution of 1:4 does correlate with disease protection, many regulatory authorities prefer the use of an 1:8 threshold as a surrogate measurement of protection, given the variability of biological assays.

"The purpose of this study was to assess the safety and immunogenicity of a quadrivalent vaccine, MenACWY-CRM, currently licensed for use from 11 to 55 years of age, in children 2-10 years of age in comparison with a quadrivalent vaccine (MCV4) already licensed in this younger age group," the authors observed. "Data from this study... now demonstrate the safety and immunogenicity of MenACWY-CRM across the age spectrum from infancy to 55 years of age."

Vaccinating pregnant women against influenza prevents hospitalization of infants under 6 months of age for influenza

Benowitz et al. Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. Clin Infect Dis *2010;51(12):1355-61.*

Vaccinating pregnant women against influenza during the influenza season is highly effective in preventing hospitalization of infants for influenza in the first 6 months of life, according to a US-based study.

Dr. Isaac Benowitz, Yale University School of Medicine, New Haven, Connecticut, carried out a matched case-control study of infants at Yale-New Haven Children's Hospital, a large urban hospital in the northeastern US. The aim of the study was to assess the effectiveness of the influenza vaccine given to pregnant women during the influenza season in decreasing laboratory-documented influenza hospitalizations among their infants. "Subjects were infants aged <12 months who were hospitalized for laboratory-confirmed influenza between October 2000 and April 2009 (prior to the arrival of the 2009 pandemic influenza in this region)," the authors observed. For each case, investigators enrolled 1 or 2 matched control infants who were also hospitalized but who were negative for influenza.

Between October 2000 and April 2009, 220 eligible infants under the age of 12 months were hospitalized for influenza, of whom 157 were enrolled in the study. Of these infants, approximately 83% were infected with influenza A while about 17% were infected with influenza B—none were infected with the 2009 pandemic influenza A H1N1, as the authors pointed out. Eighty-one per cent of infants hospitalized for influenza over the study interval were under 6 months of age.

The mothers of 2 (2.2%) of 91 case subjects, 31 (19.9%) of 156 control subjects aged <6 months, mothers of 1 (4.6%) of 22 case subjects and 2 (5.6%) of 36 control subjects aged >6 months had received influenza vaccine during pregnancy. This gave an unadjusted effective rate of 90.7% for the prevention of hospitalization for influenza among infants under 6 months of age. Adjusted for various confounders, the adjusted effectiveness of the vaccine was found to be 91.5% for this age group.

The median clinical severity score of infants hospitalized for influenza was 4 on a scale of 0 to 16 but 11 infants required admission to the ICU and infants ≥6 months at the time of hospitalization had a significantly higher mean severity score than infants <6 months (6.3 vs. 4.1). Infants with chronic medical conditions had higher severity scores than those without. "These results have great clinical relevance because they provide a strategy to confer protection to young infants at high risk for the disease and for whom no vaccine is currently available," investigators stated.

Furthermore, they added, vaccination protects their mothers who are in the high-risk category for severe influenza. The public health implications of these findings are also important, investigators noted, because a strategy of protecting an infant through vaccination during pregnancy may serve as an incentive for pregnant women to accept the influenza vaccine and for their care providers to offer it.

Herpes zoster significantly affects QoL, functional status across all age groups

Drolet et al. The impact of herpes zoster and postherpetic neuralgia on health-related QoL: A prospective study. CMAJ *2010;182(16):1731-36.*

Acute herpes zoster (HZ) significantly affects quality of life (QoL) and functional status across all age groups and changes in QoL over time closely correlate with pain severity, according to a prospective Canadian study.

Mélanie Drolet, PhD, Université Laval, Quebec City, Quebec, and multicentre colleagues described the impact of HZ and postherpetic neuralgia (PHN) on health-related QoL. "From October 2005 to July 2006, 261 outpatients aged 50 years or older with HZ were recruited from the clinical practices of 83 physicians within 14 days after rash onset," they wrote. Pain and discomfort related to HZ were measured with the Zoster Brief Pain inventory while the EuroQoL EQ-5D was used to measure QoL. Outcomes were assessed at recruitment and at multiple time points out to 180 days' post-recruitment. Of the 261 patients, 215 completed all 10 questionnaires. As the authors noted, almost all participants (88.9%) were initially treated with antiviral medication; 4.6% were immunocompromised.

At recruitment, 83.5% reported moderate to severe pain at a score of ≥3 out of 10, while their QoL EQ-5D score was 0.59 compared with 0.78 for a Canadian age-and sex-adjusted population—a difference between the 2 groups that "greatly

exceeds" a cut-off of 0.07 for minimally important differences, as the authors pointed out. "Acute pain from HZ greatly interfered with the activities of daily living," researchers noted, ["with"] more than half of participants report[ing] interference scores of 5 or greater at recruitment in the areas of sleep (63.9%), enjoyment of life (58.2%) and general activities (52.6%)."

The median duration of interference with activities of daily living because of pain varied depending on which activity was assessed but was consistent with the median duration of pain from HZ at 32.5 days. The mean EQ-5D score also increased significantly during the first 30 days by 0.042 points/week and continued to increase, albeit at a slower rate, between 30 and 90 days; for participants who reported clinically significant pain at each follow-up point, the mean EQ-5D score remained constant at 0.67 as long as pain persisted.

Importantly, 24.1% of this group of patients evolved to PHN. Patients >70 years were significantly more likely to develop PHN (32.9%) than patients between the ages of 50 and 60 (16.8%). A high proportion of patients with PHN reported not only pain and discomfort but also symptoms of anxiety or depression as well as problems with mobility and self-care throughout the postherpetic period.

"These data reinforce the need for effective preventive strategies such as vaccination, and additional early intervention to reduce the burden of HZ and PHZ," researchers concluded.

The average lifetime risk of HZ in developed countries is estimated to be about 30% and increases with increasing life expectancy.

Vaccine-preventable diseases significantly contribute to morbidity, potential mortality in travellers

Boggild et al. Vaccine preventable disease in returned international travellers: Results from the GeoSentinel Surveillance Network. Vaccine *2010;28:7389-95.*

Vaccine-preventable diseases (VPDs) significantly contribute to the morbidity and potential mortality in travellers and high rates of hospitalization among travellers who return home ill make them ideal candidates for pre-travel intervention.

Dr. Andrea Boggild, UHN-Toronto General Hospital, Ontario, and multicentre colleagues analyzed VPDs among travellers entered into the GeoSentinel Surveillance Network database. The GeoSentinel Surveillance Network comprises 49 specialized travel/tropical medicine clinics on 6 continents. "All returning travellers who attended a GeoSentinel clinic between March 1997 and December 2007 and whose final diagnosis was probable or confirmed were eligible for analysis," the authors wrote.

Among ill returned travellers, 37,542 fulfilled the inclusion criteria; of these, 580 subjects from 36 different GeoSentinel sites had a final confirmed (503) or probable (77) VPD. The most common VPDs recorded were enteric (typhoid and paratyphoid) fever (n=276); acute viral hepatitis (n=148; hepatitis A=97; hepatitis B=51); influenza (n=70); measles (n=12); pertussis (n=10); and bacterial meningitis (n=10). There were 3 deaths, one each due to enteric fever, pneumococcal meningitis and rabies. "At least 55% of those with VPDs were managed as inpatients," investigators added.

Interestingly, business travel was associated with influenza while longer travel was associated with hepatitis A infection. Overall, investigators found that younger age, male gender and travellers visiting friends and relatives, particularly to South Central Asia, all emerged as independent risk factors for VPDs. "Birth or residence in Italy or Japan also predicted VPDs," they added, "and this is potentially important information for clinicians in these countries, especially because both Italy and Japan are among the top 10 contributors to international tourism expenditures."

Notable as well, almost 30% of travellers who acquired VPDs had had a pre-travel medical consultation. "That cases of hepatitis A, varicella and measles were acquired despite pre-travel consultation speaks to a potentially lost opportunity for intervention, given the high efficacy of these vaccines," the authors observed. They added that the "highly efficacious hepatitis B vaccine" would have likely prevented most cases of hepatitis B in returned travellers as well.

"Our results underscore the importance of vaccination against enteric fever, especially for travellers to South Central Asia, and for those travelling [to visit friends and relatives]," the authors concluded, "while business travellers constitute a risk group for acquisition of influenza and this should be considered by employers and physicians alike."

Influenza vaccination has a modest but significant effect on the need to hospitalize older adults for pneumonia, influenza

Baxter R, Ray T, Fireman B. Effect of influenza vaccination on hospitalizations in persons aged 50 and older. Vaccine *2010;28:7267-72.*

Influenza vaccination has a modest but significant effect on the need to hospitalize patients 50 years of age and older for either pneumonia or influenza, according to a large-scale Kaiser Permanente study carried out in Northern California.

Dr. Roger Baxter and colleagues from the Kaiser Permanente Vaccine Study Center, Oakland, carried out a retrospective population-based study using a "difference-in-differences" approach to determine the association between hospitalization and prior vaccination in older adults. "Hospitalization, particularly from pneumonia and influenza, has been considered a marker of influenza activity and burden," they noted, "and lowering this burden is one of the goals of influenza vaccination."

During the 11 influenza years studied, there were 68,000 pneumonia and influenza hospitalizations in over 10 million person-years. Across all years, vaccination coverage averaged about 65% for persons 65 years of age and older, and 24 to30% for persons 50 to <65 years of age. "Over the 11-year period, we estimated that, during the influenza season, influenza vaccination prevented 8.5% of hospitalizations for pneumonia and influenza in persons 65 and older, and 12.4% in those 50 to 64 years of age," they reported.

In contrast, they found no effect of influenza vaccination on hospitalization for congestive heart failure, ischemic heart disease, cerebrovascular disease or trauma. As the authors noted, because most hospitalizations for pneumonia and influenza occurred in patients 75 years and older, they analyzed data separately stratified by age.

Based on this analysis, they found that vaccine efficacy among individuals between 65 and 74 years of age was 16%, while for those 75 years of age and older, vaccine efficacy was 5%. The authors in turn explained that their vaccine efficacy estimates represent the per cent of all-cause pneumonia and influenza hospitalizations occurring during influenza season that are assumed to be prevented by the vaccine.

"In persons aged 65 years and older, we estimated that, in the absence of vaccination, 30% of pneumonia and influenza hospitalizations during influenza seasons are attributable to the

influenza virus," they wrote. "Therefore our findings suggest that the 8.5% vaccine efficacy estimate in the elderly amounts to a 28% reduction in influenza-attributable hospitalizations. The corresponding reduction for persons over 50 to 64 years of age was 48%."

The authors cautioned, however, that vaccine effectiveness might vary according to the severity of the influenza season and the match of the vaccines to the circulating strains of the virus.

CPS now recommends routine rotavirus vaccination for age-appropriate infants

Salvadori M, Le Saux N; Canadian Paediatric Society, Infectious Diseases and Immunization Committee. Recommendations for the use of rotavirus vaccines in infants. Paediatr Child Health *2010;15(8):519-23.*

Routine rotavirus vaccination is now recommended for all age-appropriate infants, according to a position statement from the Canadian Paediatric Society (CPS).

As Salvadori et al. wrote on behalf of the CPS, Infectious Diseases and Immunization Committee, all children will experience at least one episode of rotavirus infection by 5 years of age. "Because rotavirus gastroenteritis is not a nationally notifiable disease, the exact prevalence and associated disease burden are not known," they pointed out.

However, it is estimated that 1 in 62 to 1 in 312 children under the age of 5 will be hospitalized with rotavirus infection, with more than half of them occurring in younger infants between the ages of 6 and 24 months. In one study cited by the authors, 60% of children attending Toronto-based child care centres sought medical care for diarrhea over an 8-month period; 17% went on to visit an emergency room (ER) and 6% were hospitalized or received intravenous hydration in the ER for diarrheal illnesses.

According to estimates provided by the Rotavirus Gastroenteritis Cohort Model, 1 in 7 Canadian children under the age of 5 will seek health care, 1 in 20 will visit an ER or be hospitalized and 1 in 62 will be hospitalized for rotavirus gastroenteritis. Premature infants are at an increased risk of rotavirus infection, they added, partly because they lack transplacental maternal antibodies.

There are currently 2 vaccines authorized for use in Canada for the prevention of rotavirus gastroenteritis in infants 6 to 32 weeks of age. As the authors pointed out, both vaccines are safe and effective and both are recommended for all infants as they significantly decrease the incidence and morbidity associated with rotavirus infection. "These vaccines may not prevent all cases of rotavirus diarrhea," the authors noted, "but they do prevent severe disease and significantly decrease the risk of dehydration and hospitalization in vaccinated infants." They cautioned, however, that since there are no interchangeability data, the rotavirus vaccination series should be completed with the same product wherever possible.

Key among their recommendations are:

- Vaccination must be started between 6 and 14 weeks plus 6 days of age, with the series completed by 8 months of age.
- Adherence to recommendations regarding the time of administration should be ensured because the safety of rotavirus vaccine administration outside of these recommendations is unknown.
- Canadian physicians should advocate for universal funding and integration of this vaccine into provincial programs to ensure equitable access for all children.
- Advocating for the availability of rotavirus vaccination programs in the developing world should be a priority because the impact on global childhood mortality and morbidity due to rotavirus infections in this context is expected to be the greatest.

The National Advisory Committee on Immunization (NACI) made the same recommendations in July 2010, adding that preterm infants between 6 weeks and 0 days and 8 months age (8 months plus 0 days) who are healthy and not hospitalized can also receive either vaccine; is the first dose given between 6 weeks and 0 days and up to 15 weeks (14 weeks plus 6 days). The vaccination series should again be completed by 8 months and 0 days.

For infants with suspected or known immunocompromising conditions, NACI does not recommend either vaccine without prior consultation with a specialist or expert . Infants with a history of intussusceptions should not be given either vaccine. □

UPCOMING EVENTS

1st International Conference on Controversies in Vaccination in Adults
January 27-30, 2011 / Berlin, Germany
http://www.comtecmed.com/CoVACc/2011/

3rd International Meeting on Emerging Diseases and Surveillance
February 4-7, 2011 / Vienna, Austria
http://imed.isid.org

45th National Immunization Conference
March 28-31, 2011 / Washington, D.C.
http://www.cdc.gov/vaccines/events/nic/

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