September/October 2008

VACCINE RESOURCE LINE

A MONTHLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

Cost-effectiveness of HPV vaccination optimized by universal coverage of young adolescent girls and targeted catch-up

Kim JJ, Goldie SJ. Health and economic implications of HPV vaccination in the United States. N Engl J Med *2008;359(8):821-32.*
Chesson et al. The potential health and economic benefits of preventing recurrent respiratory papillomatosis through quadrivalent human papillomavirus vaccination. Vaccine *2008;26(35):4513-8.*

The cost-effectiveness of vaccinating girls against human papillomavirus (HPV) in the US will probably be optimized by achieving universal coverage in young adolescent girls and by targeting initial catch-up efforts to adolescents under the age of 21, according to US researchers.

Drs. Jane Kim and Sue Goldie, Harvard School of Public Health, Boston, Massachusetts, compared the health and economic outcomes of vaccinating girls at 12 years of age and of temporary catch-up programs. "We considered the dynamics of HPV transmission, the duration of vaccine efficacy, the potential benefits of preventing noncervical HPV-related conditions, the anticipated changes in screening practice and potential disparities in access to care," they explained.

In the context of current screening and assuming lifelong vaccine-induced immunity against HPV infection, routine vaccination of 12-year-old girls had an incremental cost-effectiveness ratio of $43,600 per quality-adjusted life-year (QALY) gained compared with screening alone. "The addition of a five-year catch-up program for girls between the ages of 13 and 18 years cost $97,300/QALY and extension to 21 years of age cost $120,400/QALY," they added. The extension of the catch-up program to 26 years of age cost $152,700/QALY.

Importantly, however, inclusion of protection against HPV-6 and HPV-11-related genital warts reduced the cost per QALY by 20% to $34,900 for preadolescent girls. For catch-up to 18 years of age, QALY was reduced by 17% to $81,000 and for catch-up to 21 years of age, inclusion of protection against HPV-6 and -11 disease reduced QALY by 16% to $101,300. The cost per QALY for catch-up to 26 years of age was reduced by 13% to $133,600 using the same inclusion criteria. "Vaccination against HPV-16 and HPV-18 is expected to be economically attractive [i.e.<$50,000/QALY], if high coverage can be achieved in the primary target group of 12-year-old girls and if vaccination-induced immunity is lifelong," the authors stated. Under these conditions, they added, a catch-up program for girls between the ages of 13 and 18 also appears to be reasonable provided society is willing to pay $100,000/QALY, "especially when we include the benefits of averting genital warts [with the use of the quadrivalent vaccine] or the benefits of cross-protection against other high-risk types of HPV not including HPV-16 and HPV-18 [as reported with the bivalent vaccine]."

A separate analysis estimated the health and economic benefits of preventing recurrent respiratory papillomatosis (RRP) through vaccination with the quadrivalent HPV vaccine. Analyses showed that the inclusion of the potential benefits of preventing RRP in children of vaccinated mothers could change the estimated impact and cost-effectiveness of quadrivalent HPV vaccination of 12-year-old girls, although the magnitude of this change varied substantially. For example, under base case assumptions (i.e. vaccination of 12-year-old girls in the US vs. no vaccination, costs and benefits being calculated per girl vaccinated), the inclusion of RRP lowered the estimated cost per QALY gained by about 14% in the intermediate- and high-cost per QALY scenario and by approximately 21% in the low-cost per QALY scenario. However, by varying three RRP-related parameters (incidence, cost and QALYs lost per case of RRP), "the percentage reduction in the cost per QALY ranged from 2% to >100% in the low-cost QALY scenario and from 1% to >65% in the intermediate- and high-cost per QALY scenarios," the authors reported. "Thus," they concluded, "the impact of including the benefits of preventing RRP on the estimated cost-effectiveness of HPV vaccination could be minimal or could be substantial, depending on the assumptions regarding RRP incidence, cost and lost QALYs."

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Herpes zoster vaccine approved

Globe and Mail, Wednesday, August 27, 2008. Page A9.

As reported recently in the *Globe and Mail*, the long-awaited herpes zoster (HZ) vaccine has been approved by Health Canada for patients ≥60 years of age. It is expected that the vaccine will be available for physicians to immunize older Canadians against reactivation of the varicella virus later next year. The vaccine received approval from Health Canada based on results from the Shingles Prevention Study, which demonstrated that a single dose of the HZ vaccine prevented over 50% of acute zoster episodes in this patient population, and reduced the incidence of post-herpetic neuralgia by two-thirds relative to placebo.

CDC reports marked reduction in rotavirus disease following introduction of rotavirus vaccine

CDC MMWR *2008;57(25):697-700.*

In the US, it is estimated that RV diarrhea is responsible for 55,000 to 70,000 hospitalizations, more than 200,000 emergency room visits, approximately 400,000 physician visits annually and approximately 20 to 60 deaths per year among children under 5 years old. It also costs an estimated $1 billion or more in direct and indirect costs, including lost work time for parents, in the US alone.

This year, the Centers for Disease Control and Prevention (CDC) has reported a highly significant reduction in the incidence of rotavirus (RV) disease and associated medical care following introduction of the oral pentavalent RV vaccine compared to previous years.

Data from two different surveillance systems showed that there was a marked reduction in the number of positive laboratory tests for RV gastroenteritis and associated medical care including hospitalizations, emergency room and clinic visits in the 2008 RV season compared to previous years. "Data are preliminary," noted Dr. Mary Allen Staat, Professor of Pediatrics, University of Cincinnati, Ohio, whose Children's Hospital Medical Center is participating as a primary CDC RV surveillance site. "But as a pediatrician, I am excited about the marked reduction in RV disease we saw this season which coincided with increasing uptake of [the RV vaccine]."

In one analysis, only 18% of samples tested were positive for RV in the 2007-2008 RV season compared with a median of 41% for the previous seasons combined (July 1991 through June 2006). Results were based on data from the National Respiratory and Enteric Virus Surveillance System.

In the second analysis, data showed a marked reduction in hospitalizations and emergency room and clinic visits due to RV gastroenteritis during 2008 compared with 2006 and 2007. Among those children who presented to hospitals, emergency rooms or outpatient clinics with acute gastroenteritis, 207 patients had RV gastroenteritis in 2006, 259 in 2007, and only 18 in 2008. The overall proportion of fecal samples from the children who tested positive for RV was approximately 51% in 2006 and 54% in 2007, with a significant reduction to 6% in 2008. Results were based on data from the New Vaccine Surveillance Network, which conducts population-based surveillance in three US counties for RV gastroenteritis among children <3 years of age.

Many children likely excluded from receiving the new rotavirus vaccine: Philadelphia experience

Daskalaki et al. Implementation of rotavirus immunization in Philadelphia, Pennsylvania: High levels of vaccine ineligibility and off-label use. Pediatrics *2008;122(1):e33-e8.*

A substantial proportion of children are likely excluded from receiving even a single dose of the new pentavalent rotavirus vaccine (PRV) or from completing the series, according to an analysis of the first six months of its use in Philadelphia, Pennsylvania.

Dr. Irini Daskalaki, St. Christopher's Hospital for Children, Philadelphia, and colleagues from various institutions in the area examined whether the current narrowly-defined age limits for the PRV exclude children from completing immunization against rotavirus. At the same time, they assessed adherence (off-label use) of health care providers to the recommended age limits for the PRV, in particular age <12 weeks for series initiation and ≤32 weeks for completion of the series. "During the first six months of the implementation of PRV in Philadelphia, 110 immunization-provider sites ordered PRV through the Vaccines for Children program, 17,443 PRV doses were distributed and 5566 PRV administrations were recorded in the registry," researchers observed.

Some 3912 doses were given as first doses, 1419 as second doses and 235 as third doses. Of the 3912 first doses, 770 (19.7%) were given to children >12 weeks of age, while of the 1419 second doses, 14 (9.7%) were given to children >32 weeks of age. Of the 235 third PRV doses, 9 (3.8%) were again given to children >32 weeks of age.

As the authors pointed out, underimmunization in the first years of life has led to outbreaks of highly transmissible diseases. "Consequently, timeliness of immunizations is recognized as a factor, with growing importance in the improvement of vaccine implementation," they stated, "and in view of the novel narrowly-defined age limits for PRV, timeliness of immunization is a pressing priority."

Researchers did speculate however, that the substantial off-label use of the vaccine they observed in this study might have been due to its availability prior to the publication of guidelines detailing its use, as well as the uniquely narrow age limits set by regulatory officials for use and completion of the PRV series.

Physician peer educators do not improve quality of immunization services over routine visits alone

Taylor et al. Effectiveness of a physician peer educator in improving the quality of immunization services for young children in primary care practices. Vaccine *2008;26(33):4256-61.*

The use of physician peer educators, complete with follow-up letters and telephone calls, did not improve the quality of immunizations services provided by primary care practices over routine educational visits, as reported in a comparative analysis of the two strategies.

Investigators under lead author Dr. James Taylor, University of Washington, Seattle, assessed the impact of having a physician peer educator present a series of slides on all aspects of vaccination, including storage and needle use, over that following a routine visit from public health departments. "The primary study outcome was practice immunization rates [PIRs] determined one year after the intervention or one year after the initial assessment in control practices," the authors observed. A total of 73 primary care practices in King County, Washington, consisting of 48 family medicine practices and 25 pediatric practices, participated in the study. Thirty-seven sites were randomized to receive the presentations by the physician peer educator (intervention group) and the remaining 37 sites served as controls.

At baseline, the mean PIR of participating practices was 68.3% and there was no significant difference in mean PIR between intervention and control practices. One year later, PIR rates in the two study groups remained similar: mean PIRs were 71.4% in the intervention sites and 69.6% in the control practices, researchers reported. At the time of initial assessment, no statistically significant differences between intervention and control practices were seen in any immunization variable. There was also a general improvement in all measures of immunization variables in both groups over the same follow-up interval. A higher proportion of practices in the intervention group used the appropriate needle length for vaccinating a two-month-old child; other than this, the proportion of intervention and control practices using evidence-based vaccine policies was not statistically significantly different.

The authors suggested that the most likely reason for the lack of difference between the intervention and control practices is that the control group actually received a substantial "intervention" themselves because all practices received a site visit by public health personnel. Thus, as this study suggests, educational efforts designed to increase immunization rates and quality in practice settings need

to focus on interventions that can be easily implemented, which can also be delivered effectively by immunization nurses and other health department personnel during regular site visits.

Profile of a new trivalent inactivated influenza vaccine

Talbot et al. Immunogenicity, safety and consistency of new trivalent inactivated influenza vaccine. Vaccine *2008;26(32):4057-61.*

A large randomized trial of a new trivalent inactivated influenza vaccine (TIV) has exceeded requirements for licensure specified by the Food and Drug Administration (FDA) and has now been approved for use in the prevention of influenza infection.

Dr. Keipp Talbot, Vanderbilt University School of Medicine and Pediatrics, Nashville, Tennessee, and multicentre colleagues carried out a phase III placebo-controlled study evaluating the immunogenicity, safety and tolerability of the new TIV in adults between the ages of 18 and 64 years of age. "The primary objectives of this study were to demonstrate that the two presentations of vaccine produced 40% seroconversion [defined as an increase in HI antibody titre of at least fourfold, with a minimum post-vaccination HI titre of 40] and 70% seroprotection [defined as a minimum post-vaccination HI titre of 40] to each of the three individual influenza antigens," the authors explained.

A total of 1357 participants received either the vaccine or placebo: 823 received a multidose vial, 266 received pre-filled, thimerosal-free syringes and 268 received placebo. The proportion of those who achieved seroprotection (post-vaccination titre >40) was 97.8% for the A/New Caledonia strain, 99.9% for the A/New York strain and 94.2% for the B/Malaysia strain. "All presentations of vaccine yielded comparable immune responses," the authors reported. In general, the adverse event profile was comparable between the thimerosal-free and thimerosal-containing preparations, but injection site pain and tenderness were more frequent with the thimerosal-free preparations.

"The new vaccine studied in this report exceeded [FDA] requirements with >90% of subjects achieving post-immunization titres of 40 [or more] for all three vaccine antigens," researchers noted, "and this immunogenic response was consistent across the three different lots of vaccine and between the two presentations, multidose vials and pre-filled syringes." The licensure of an additional influenza vaccine is "welcome," the authors commented, as it should provide additional doses of vaccine to accommodate potential vaccine shortages.

Pertussis vaccination program cost-effective for adults

Lee et al. Cost-effectiveness of adult pertussis vaccination in Germany. Vaccine *2008;26(29-30):3673-9.*

A vaccination program to prevent pertussis in adults between the ages of 20 and 64 could be cost-effective and even cost-saving if the disease incidence among adults is higher than 200 per 100,000 population, according to multicentre investigators.

Dr. Grace Lee, Harvard Medical School and Harvard Pilgrim Health Care, Boston, Massachusetts, and multicentre colleagues estimated the cost-effectiveness of vaccination in adults in Germany between 20 and 64 years of age with either a single dose of the combination vaccine with an acellular pertussis component (TdaP) or with decennial TdaP booster. "We evaluated the following strategies," the authors explained. "No adult pertussis vaccination, one-time adult pertussis vaccination at 20 to 64 years of age, where TdaP is administered instead of Td, and adult pertussis vaccination with decennial boosters."

At a disease incidence of 165 per 100,000 population of adults, approximately 4.4 million cases of pertussis would occur over the lifetime of the cohort, they observed. Analyses showed that the one-time adult vaccination strategy would potentially prevent 498,000 cases of pertussis while the adult vaccination strategy with decennial boosters would potentially prevent one million cases. Herd immunity was also incorporated into the base case analysis and when this was factored in, the one-time adult vaccination strategy was found to also prevent 178 infant cases of pertussis, the majority of which would have required hospitalization.

The cost of not having a pertussis vaccination program over the lifetime of the cohort would range from between €828 million to €7.1 billion, depending on the disease incidence, investigators added. This compared to the cost of a one-time vaccination strategy targeting 31 million people, which would total €366 million, and €687 million for a decennial booster vaccination strategy that would result in 97 million immunizations in adults. If the disease incidence were greater than 200 per 100,000 population, "adult vaccination programs become cost-saving," investigators reported. At a low disease incidence of 50 per 100,000 population, one-time and decennial adult vaccination programs could still save 3600 and 7500 quality-adjusted life-years, respectively.

Over 90% of children receive the primary childhood immunization series in Germany. It is also recommended that a booster shot for children and adolescents between nine and 17 years of age be administered. Despite these high rates, "pertussis has remained endemic in Germany," the authors observed, in part at least due to waning immunity in adults following childhood vaccination.

Diabetes increases risk of pneumonia-related hospitalization

Kornum et al. Diabetes, glycemic control, and risk of hospitalization with pneumonia: a population-based case-control study. Diabetes Care *2008;31(8):1541-5.*

According to a recent report, both type 1 and type 2 diabetes significantly increase the risk of patients needing to be hospitalized for pneumonia and poor long-term glycemic control increases this risk even further.

Dr. Jette Kornum, Aarhus University Hospital, Denmark, and colleagues carried out a population-based, case-control study during which they identified patients with a first-time, pneumonia-related hospitalization between 1997 and 2005. "For each case, 10 sex- and-age-matched population control subjects were selected from Denmark's Civic Registration System," they noted.

Compared to nondiabetic controls, the adjusted relative risk for pneumonia-related hospitalization for patients with diabetes was 1.26. For type 1 diabetic patients, the adjusted relative risk for a pneumonia-related hospitalization was 4.43, or a 4.4-fold increased risk compared with nondiabetic controls. For those with type 2 diabetes, the adjusted relative risk was 1.23, or a 1.2-fold increased risk of patients requiring hospitalization for pneumonia compared to those without diabetes.

Duration of diabetes of ≥10 years also significantly increased the risk of patients requiring a pneumonia-related hospitalization, as did poor glycemic control. For example, patients with diabetes with an A_{1c} level of ≥9% had a 60% greater risk of requiring a pneumonia-related hospitalization vs. nondiabetic controls while those with diabetes plus an A_{1c} of <7% still had a 22% increased risk compared with nondiabetic controls.

"Our data, combined with previous results, provide strong evidence that diabetes is associated with a 25% to 75% increase in the relative risk of pneumonia-related hospitalization," researchers concluded, "and these results emphasize the value of influenza and pneumococcal immunization, particularly for patients with longer diabetes duration as well as the importance of improved glycemic control."

New adolescent vaccines spark renewed interest in adolescent immunization

Brabin et al. Current issues in adolescent immunization. Vaccine *2008;26(33):4120-34.*

The recent introduction of several new vaccines targeted to adolescents has sparked renewed interest in adolescent immunization as a strategy to improve their lives as well as of those they come into contact with.

Dr. Loretta Brabin, Women's Health, University of Manchester, UK, and multicentre colleagues summarized proceedings from a symposium entitled "Adolescent Immunization: From Science to Health Policy," held in Annecy, France, in December 2006. In their manuscript, they noted that the development of the meningococcal conjugate vaccine (MCV4), TdaP and human papillomavirus (HPV) has revitalized interest in adolescent immunization, given the substantial benefits already demonstrated by examples such as Italy following the introduction of the hepatitis B (HBV) vaccine program for young recipients.

Prior to launching its program in 1991, Italy was considered to have medium HBV endemicity and it was felt that the pool of chronic HBV carriers most likely arose from individuals infected in childhood. To decrease the number of susceptible children who were at high risk for acquiring chronic HBV infection, Italy adopted a program that included not only universal infant immunization but also adolescent immunization against HBV, researchers pointed out. Since then, no clinically overt hepatitis has been detected in vaccinated individuals and Italy is now considered a country with low HBV endemicity.

Other examples of worthwhile vaccination initiatives among adolescents include vaccination against invasive meningococcal disease where adolescents have a higher case-fatality rate of 22.5% than infants and children, whose case-fatality rate is 4.6%. Adolescent pertussis infections cause not only significant morbidity to adolescent themselves, the authors observed, but "they pose an even greater risk to society." The World Health Organization in fact recommends additional vaccinations against diseases such as pertussis in order to maintain or increase the duration of effective protection derived from prior childhood vaccinations.

HPV is a common infection often contracted soon after sexual debut, researchers noted. With two HPV vaccines now available, transmission of HPV—known to cause almost all genital warts and at least 70% of cervical cancers—could be radically reduced. As the authors observed, understanding and addressing perceptions of adolescent immunization among adolescents, their parents and health care providers is an important part of overcoming barriers to program implementation. "For example," they noted, "given that a number of current and future vaccines are targeted at sexually-transmitted infections [STIs], potential controversy regarding adolescents and sexual issues may shroud vaccines' individual and public health benefits." Adolescents, parents and health care providers therefore need to "hear the message" that to be most effective, vaccination against STIs, including HPV and HBV, must occur before sexual activity, they added.

"Clearly, vaccinating adolescents can provide substantial health benefits to the individual, society and future generations," investigators concluded. "The true value of vaccination is often not fully appreciated." ❑

UPCOMING EVENTS

2nd Congress of the European Academy of Paediatrics
October 24-28, 2008 / Nice, France

Joint Meeting of the 48th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and 46th Annual Meeting of the Infectious Diseases Society of America (IDSA)
October 25-28, 2008 / Washington, DC

Eurogin 2008
November 9-12, 2008 / Paris, France

Understanding and Controlling Infectious Diseases: An Agenda for the 21st Century
November 11-13, 2008 / Paris, France

21st Annual Infectious Diseases in Children Symposium
November 22-23, 2008 / New York, New York

8th Canadian Immunization Conference
November 30-December 3, 2008 / Toronto, Ontario

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