March-April 2008

VACCINE RESOURCE LINE

A MONTHLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

Cost-effectiveness of a catch-up meningococcal vaccine program

Ortega-Sánchez et al. Economics of an adolescent meningococcal conjugate vaccination catch-up campaign in the United States.
Clin Infect Dis *2008;46(1):1-13.*

Catch-up and routine vaccination of adolescents, although costly, could have a substantial impact on meningococcal disease burden in the US, cutting the number of cases by almost half over a 10-year period.

Dr. Ismael Ortega-Sánchez, National Centers for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Bethesda, Maryland, and colleagues analyzed the cost-effectiveness of a catch-up vaccination program in which most children and adolescents between the ages of 11 and 17 would be vaccinated with the meningococcal conjugate vaccine (MCV4) within one year of initiating the campaign. This would be followed by routine vaccination of successive cohorts of children at the age of 11 over the next nine years. Investigators assessed both the direct benefits of vaccination vs. no vaccination, along with the effect that herd immunity could be expected to have on disease burden, based on experience with routine meningococcal vaccination in the UK.

With no vaccination, an average of 1674 cases of meningococcal disease attributable to serogroups C, Y and W135 would occur each year in the US. The proposed catch-up program would avert a mean of 156 cases per year from direct protection alone. "With herd immunity, the program would increase the annual number of cases averted to 825 [a 48% reduction]," the authors noted—suggesting that almost four-fifths of all prevented cases of meningococcal disease would be attributable to herd immunity. Assuming full herd immunity, the same catch-up strategy would prevent 8251 cases over 10 years, they added.

With regards to net returns and costs, investigators calculated that their proposed catch-up and routine vaccination program would save $551 million in direct costs (excluding program costs) and $920 million in indirect costs. At an estimated cost of $83 for each child and adolescent vaccinated, the entire catch-up and routine vaccination program would cost approximately $223,000 per case of meningococcal disease averted; approximately $2.6 million per death prevented; approximately $127,000 per life-year saved; and approximately $88,000 per quality-adjusted life-year saved.

"Vaccination of adolescents in a combined publicly-funded catch-up and routine vaccination program with MCV4 would result in net economic costs to society, even under the most optimistic scenarios," investigators acknowledged. "However, such a program holds the greatest promise for substantial and quick reduction in overall meningococcal disease burden in the US."

Investigators also noted that if the same catch-up vaccination strategy were to be introduced in countries where meningococcal disease is highly endemic, it would be three times more cost-effective than the same program in the US.

NACI revises meningococcal C conjugate vaccine schedule for infants

Concerns regarding the duration of protection following the previously recommended infant meningococcal C conjugate vaccination schedule has led to revised recommendations for infant and toddler vaccinations. A recent National Advisory Committee on Immunization (NACI) statement now recommends that if the meningococcal C conjugate vaccine is given to infants under 12 months of age, a booster dose should be given between the ages of 12 and 23 months. NACI also suggests that a dose at 12 to 18 months would be a convenient time to provide this booster. This new recommendation replaces the previous one indicating that a single dose of the vaccine be given after five months of age.

Genital warts significantly affect quality of life: UK study

Woodhall et al. Estimation of the impact of genital warts on health-related quality of life.
Sex Transm Infect *2008 Mar 13 (Epub).*

Genital warts significantly affect quality of life, according to a UK study, and authors suggested that their prevention should be factored into decisions as to which vaccine should be introduced into public health programs to prevent infection against the human papillomavirus (HPV).

Dr. Sarah Woodhall, University of York, UK, and multicentre colleagues analyzed the impact of genital warts on health-related quality of life in men and women attending the York Genitourinary Medicine clinic for treatment. Members of the research team assessed the impact of having genital warts among 81 patients using several different health-related questionnaires and compared scores with control subjects of the same age.

"When asked whether genital warts affected their quality of life, almost half of the cases answered 'significantly' or 'very

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significantly,'" the authors reported. On the EQ visual analog score (VAS), for example, patients with genital warts scored an average of 13.9 points lower than controls, a significant difference between the two groups. "Young women in the sample exhibited lower EQ VAS scores than men of the same age," the authors added.

As researchers pointed out, the majority of the detriment to health-related quality of life by having a diagnosis of genital warts was associated with the dimension of anxiety and depression. "This is consistent with what is known about the experience of genital warts, in that most of the associated morbidity is thought to be psychological," they explained. Nevertheless, this was the first study to actually use standardized measures of health-related quality of life in patients with genital warts in the UK.

Having found that a diagnosis of genital warts indeed does carry a "substantial" burden of disease, "the potential added benefit of preventing the majority of cases of genital warts by HPV vaccination should be considered in decisions about which HPV vaccine to implement in the UK," researchers concluded. In October of last year, public health officials in the UK announced they would initiate a HPV immunization program targeting 12- to 13-year-old girls in September 2008. Of the two new HPV vaccines that are currently available, only the vaccine that prevents infection by HPV types 6 and 11, estimated to cause over 95% of genital warts, will reduce the burden of disease associated with genital wart infection.

No association between MMR vaccination and autism spectrum disorders

Baird et al. Measles vaccination and antibody response in autism spectrum disorders. Arch Dis Child *2008 Feb 5 [Epub].*

The third virological, case-controlled study exploring a possible link between the measles-mumps-rubella (MMR) vaccine and autism spectrum disorders (ASD) has again failed to find any evidence that the vaccine is involved in the pathogenesis of ASD, based on data from the largest sample size to date.

Dr. Gillian Baird, Guy's Hospital, London, UK, and multicentre colleagues took advantage of SNAP (Special Needs and Autism Project), a new geographically-defined study of the prevalence of ASD, to test the hypothesis that MMR vaccination is involved in ASD pathogenesis, as reflected by signs of a persistent measles infection or abnormally persistent immune responses in MMR-vaccinated children compared with controls. Researchers also studied children with ASD and a history of regression. The initial cohort consisted of 56,946 children born between July 1, 1990, and December 31, 1991, in 12 districts in the South Thames region of the UK.

Following an elaborate screening process, investigators identified a community sample of 98 vaccinated children between the ages of 10 and 12 who had been diagnosed with ASD. They compared measles antibody responses with those from two control groups, one with special educational needs but no ASD (n=52) and another group of 90 children who were developmentally normal. All were tested for the presence of measles virus as well as antibody response to the measles vaccine in serum.

Test results on measles virus assays found no difference between either circulating measles genome or measles antibody concentrations in both children with ASD and controls. Additionally, there was no evidence of an altered, persisting immunological response following either one or two MMR vaccinations in ASD children with and without a history of regression. "Only one child had symptoms of possible enterocolitis, and this child was in the control group," researchers observed.

The authors also noted that in the cohort overall, children were significantly less likely to receive a second MMR vaccination following a diagnosis of a developmental problem. This observation is in line with a trend, at least in the UK, for lower uptake of the MMR vaccine in general because of public concern about a putative link between MMR vaccination and ASD. To date, neither epidemiological nor virological evidence supports any link between MMR vaccination and ASD, researchers stressed.

Recent studies have placed the prevalence rates of ASD at between six and 12 per thousand, significantly higher than previous estimates, depending on the strictness with which diagnostic criteria are applied.

Risk of HPV infection is high in young women who have sex with only one male

Winer et al. Risk of female human papillomavirus acquisition associated with first male sex partner. J Infect Dis *2008;197(2):279-82.*

Almost 30% of young women who have sex with only one male partner are infected with the human papillomavirus (HPV) within a year, and almost 50% of women are infected by three years, according to a single-centre report.

Dr. Rachel Winer, University of Washington, Seattle, and colleagues recruited 244 female university students between the ages of 18 and 22 years who were eligible for the longitudinal study if they had never had vaginal intercourse with a male partner or if they had first had sex with a male partner within the previous three months. Women received a gynecological exam every four months and swabs were collected for HPV DNA testing by PCR-based methods. The analysis was restricted to 130 women who reported first intercourse within three months of enrolment or during follow-up and who had at least one clinical visit after first intercourse.

The mean age of the 130 women was 19.4 as assessed at the date of first intercourse, while the mean age of their first male partner was 21. After first intercourse, the mean follow-up was 28.2 months. "The 12-month cumulative incidence of first HPV infection after reporting a first sex partner was 28.5%," investigators reported, "and [this] increased to 39.2%... at 24 months and to 49.1%... at 36 months." The mean number of HPV types detected at the time of first HPV infection was 1.5. On multivariate modelling, the only variable that predicted HPV infection was the male's number of previous partners.

"The percentage of university-aged women who acquired an HPV infection from a first male sex partner was high and the risk increased when the partner was sexually experienced," investigators concluded. "These results indicate that women are at high risk of acquiring an HPV infection from just one male sex partner."

HAV/HB vaccine recipients develop protective antibodies to both infections over extended follow-up

Díaz-Mitoma et al. Long-term antibody persistence induced by a combined hepatitis A and B vaccine in children and adolescents. Vaccine *2008;26(14):1759-63.*

Children and adolescents who receive the recommended schedule of the combined hepatitis A (HAV) and hepatitis B (HB) vaccine develop protective antibodies to both infections over an extended follow-up of up to 10 years.

Dr. Francisco Díaz-Mitoma, Children's Hospital of Eastern Ontario, Ottawa, and multicentre colleagues followed two cohorts of children who had received the combined HAV/HB vaccine (pediatric formulation) for up to 7.5 years in one group between the ages of one and six years at the time of vaccination and up to 10 years in a second group between the ages of six and 15 years at the time of vaccination. One month

after primary vaccination, all recipients became seropositive for anti-HAV antibodies and anti-HB antibodies.

Over long-term follow-up, investigators again found that 100% of both age cohorts remained anti-HAV-seropositive, while 86.5% of the younger cohort and 95.5% of those in the older cohort still had persistent immunity against HB. "The persistence of anti-HAV and anti-HB antibody concentrations after the combined vaccine is similar to that observed with the corresponding monovalent vaccines which are associated with eliciting an immune response that is [both] long-lasting and [similar] to that observed in adults," investigators reported.

Furthermore, mathematical modelling of HAV persistence suggests that detectable levels of anti-HAV antibodies persist for as long as 20 to 25 years after administration of the last dose of the monovalent HAV vaccine. "Based on these facts, it can be assumed that a booster dose is not necessary even in individuals who do not have detectable levels of anti-HAV antibodies," investigators suggested.

Regarding HB, the group noted that a recent Italian study of healthy adolescents showed that over 90% of recipients of the monovalent HB vaccine had seroprotective levels of anti-HB antibodies 11 years later. Results in the current study are "in line" with those reported by Italian investigators, the authors of the current study indicated, and suggested that the dual vaccine would provide long-term immunogenicity against HB as well, although the sample size in this particular study was felt to be too small to make any definite conclusions.

"Well-tolerated and immunogenic monovalent vaccines exist against both infections," they observed. "However, the combination of HAV and HB vaccination offers many advantages, including convenience and compliance of subjects and cost savings for controlling the diseases."

Oral sucrose solution effective analgesic when given prior to routine immunization

Hatfield et al. Analgesic properties of oral sucrose during routine immunizations at 2 and 4 months of age.
Pediatrics *2008;121(2):e327-34.*

According to a multicentre American study, giving infants an oral sucrose solution two minutes before routine immunization effectively decreases injection pain compared with placebo controls.

Dr. Linda Hatfield, Pennsylvania State University of Nursing, Philadelphia, and multicentre colleagues evaluated the analgesic properties of an oral sucrose solution during routine immunization in infants between two and four months of age. One hundred healthy term infants were randomly stratified into two- or four-month age groups and then further randomized to receive 2 mL of a 24% oral sucrose and pacifier or sterile water control solution. Each of the preparations was given two minutes before infants received the combined diphtheria-tetanus-acellular pertussis, inactivated polio vaccine and the hepatitis B vaccine. The *Haemophilus influenzae* type b vaccine was given three minutes after the first series of injections followed two minutes later by the pneumococcal conjugate vaccine. The University of Wisconsin Children's Hospital (UWCH) pain scale was used to measure serial acute pain responses at baseline and at two, five, seven and nine minutes after either solution was given. The UWCH pain scale is a previously validated composite pain scale for preverbal and nonverbal children.

The mean difference in pain scores between the sucrose and sterile water groups at baseline was only -0.02. This difference widened to -1.83 at two minutes, to -1.34 at five minutes and to -1.01 at seven minutes. The differences in pain scores between the two treatment groups were significant at all time points. At nine minutes, the mean difference between the two groups was again significant at -2.16. Indeed, "the group receiving sucrose returned to near normal two minutes later (i.e. at nine minutes) at 0.59, whereas the placebo group remained at 2.91 (after nine minutes), reflecting a 78.5% difference in mean pain score relative to sterile-water mean pain score," investigators reported.

Researchers added that the sucrose solution did not eliminate pain at any point in time. However, they suggested that other pain reduction or comforting measures including distracting, holding and feeding of the infant used in conjunction with sucrose administration may provide additional comfort. The 2006 immunization schedule requires that infants and toddlers receive as many as 24 injections in the first two years of life and as many as five injections at a single visit. Reluctance to adhere to the recommended schedule may be partially blamed on parental perception that their infant endures a substantial amount of pain during routine immunization.

Influenza but not pneumococcal vaccination steadily increasing in Ontario

Al-Sukhni et al. Impact of public vaccination programs on adult vaccination rates: Two examples from Ontario, Canada.
Vaccine *2008;26(11):1432-7.*

As publicly funded programs begin to pay dividends, uptake of influenza vaccination is increasingly steadily in Ontario but pneumococcal vaccination rates still remain below target for all risk groups.

Dr. Wigdan Al-Sukhni, University of Toronto, Ontario, and colleagues identified trends in vaccination coverage against influenza and pneumococcal disease among adults in the Metropolitan Toronto and Peel regions of the province. Rates were compared between 1996 (before the publicly funded programs were launched) and 2001. In 2001, Canadian national targets for influenza vaccination rates were set, with a goal of 70% for at-risk adults and of 80% for adults >65 years of age.

Goals for adult pneumococcal vaccination were set in 1998, to a target of 80% of eligible adults by 2003. In 2005, the same goal for pneumococcal vaccine was set for patients >65, to be achieved by the year 2010. To meet these targets, 12 of Canada's 13 provinces and territories developed publicly funded influenza vaccine programs, and all 13 developed publicly funded pneumococcal vaccination programs.

In 2000, Ontario announced the first free universal influenza vaccination in the world, aiming to vaccinate 60% of low-priority and 90% of high-priority individuals against influenza. To obtain data on vaccination status, 93 persons were surveyed in 1999, 31 were surveyed in 2000 and 115 were surveyed in 2002. As investigators reported, vaccination rates increased in all groups over time, including those <65 with an underlying illness, those ≥65 years of age who were otherwise healthy and those ≥65 years of age with underlying illnesses.

Conversely, only respondents ≥65 years of age met the stated coverage rate for influenza vaccination and rates for pneumococcal vaccine uptake were below target for all respondents. Interestingly, neither the respondents' income nor their level of education was associated with a greater or lesser likelihood that they would have received either vaccine. "In contrast to pediatric vaccination programs in Canada, for which 80% to 90% uptake rates are expected immediately on implementation, adult vaccination programs may not be as successful and may require ongoing assessment and promotion," investigators observed.

However, given that over 90% of unvaccinated respondents had seen a physician within the past year—and most vaccinations occurred in a physician's office—there appears to be a clear opportunity for physician advocacy to improve immunization rates, they added.

Further study of cold-adapted influenza vaccine warranted in infants under six months of age

Vesikari et al. Safety and tolerability of cold-adapted influenza vaccine, trivalent, in infants younger than 6 months of age. Pediatrics *2008;121(3):e568-73.*

Further evaluation of a cold-adapted influenza vaccine in infants under six months of age is warranted now that its safety and tolerability profile has proven to be acceptable in a small sample of infants.

Dr. Timo Vesikari, University of Tampere Medical School, Finland, and colleagues evaluated the safety and tolerability of a cold-adapted influenza vaccine, trivalent (CAIV-T), administered intranasally to healthy infants aged from six to <24 weeks of age. Infants were separated into those who were from six to <16 weeks of age and those who were between 16 and <24 weeks of age. Each group was randomly assigned to receive either two doses of the vaccine or placebo intranasally 35 days apart. Evidence of any vaccine-reactive event was monitored for 11 days after each dose, while other adverse events were monitored for 28 to 35 days after the second dose.

Of the 31 youngest infants who received the vaccine, more of them experienced irritability (66.7%) as well as runny nose or nasal congestion (63.3%) after the first dose (but not after the second) vs. 35.7% and 33.3%, respectively, for those in the placebo arm. "Similarly, in the 16- to <24-week cohort, runny nose or nasal congestion and irritability were the most frequently reported reactogenicity events among CAIV-T and placebo recipients but the incidence was similar in both treatment groups," investigators added.

Interestingly, cough was significantly more common in the placebo cohort between the ages of 16 to <24 weeks than in CAIV-T recipients. Otherwise, there were no significant increases in any other reactogenicity or adverse events in the vaccine recipients compared with placebo. As investigators noted, the most frequently reported adverse events in both age cohorts and after each dose of the vaccine were bodily discomfort, fever and rhinitis but there was no significant difference in the incidence of any of these events between the two treatment groups in either age cohort.

Because young infants are at high risk for influenza-related complications, vaccination of household contacts is currently recommended to provide indirect protection to those younger than six months, for whom vaccination is not currently recommended. "Despite a relatively small sample size, this study has demonstrated that CAIV-T was well tolerated when administered to infants six to 24 weeks of age," they noted, "and results presented here support further evaluation of CAIV-T in young infants."

The new intranasal CAIV-T vaccine is a refrigerated formulation of a live attenuated influenza vaccine.

Neutralizing antibody to Japanese encephalitis persists for up to five years in most vaccine recipients

Sohn et al. A 5-year follow-up of antibody response in children vaccinated with a single dose of live attenuated SA14-14-2 Japanese encephalitis vaccine: Immunogenicity and anamanestic responses. Vaccine *2008;26(13):1638-43.*

Neutralizing antibody to Japanese encephalitis (JE) appears to persist for up to five years in the majority of children following a single injection of a live attenuated JE vaccine.

Dr. Young Mo Sohn, Yonsei University College of Medicine, Seoul, Korea, and multicentre colleagues evaluated long-term protective immunity of the live attenuated SA14-14-2 JE vaccine both after primary vaccination as well as after a booster dose. In June 2000, a single dose of the vaccine was given to 98 children between one and 15 years of age. Prior to receiving the vaccine, 69 out of these 98 children were seronegative for JE. This group was then evaluated for antibody levels to JE in both 2004 and 2005, at which point almost 90% of them (n=62) were found to have high levels of neutralizing antibody four years after vaccination, while 44 of them remained positive in 2005, five years after receiving a single injection of the JE vaccine. Between 2004 and 2005, 24 vaccine recipients became seronegative for neutralizing antibody and were revaccinated with the same vaccine in 2006.

Seven days after receiving the booster dose, over 76% of recipients had seroconverted, suggesting that there is rapid secondary immune response shortly after a booster dose is given among those who lose their antibody response to the first dose of the vaccine.

Investigators suggested that a single dose of live JE vaccine is likely to be effective to provide long-term protection in areas where JE is endemic, where natural boosting is quite likely taking place over time. They cautioned, however, that further studies are needed to evaluate whether a single dose of the same live JE vaccine could effectively provide protective immunity in areas where JE is not endemic. ❑

UPCOMING EVENTS

18th European Congress on Clinical Microbiology and Infectious Diseases (ECCMID)
April 19-22, 2008 / Barcelona, Spain

11th Annual Conference on Vaccine Research
May 5-7, 2008 / Baltimore, Maryland

Primary Care Today
May 8-10, 2008 / Toronto, Ontario

26th Annual Meeting of the European Society for Pediatric Infectious Diseases
May 14-17, 2008 / Graz, Austria

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June 19-22, 2008 / Kuala Lumpur, Malaysia

85th Annual Meeting of the Canadian Pediatric Society (CPS)
June 24-28, 2008 / Victoria, British Columbia

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