January-February 2007

VACCINE RESOURCE LINE

A MONTHLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

Proposing compulsory HPV vaccination in preadolescent girls

Colgrove J. The ethics and politics of compulsory HPV vaccination. N Engl J Med *2006;355(23):2389-91.*

Following a proposal by Michigan state lawmakers that vaccination against HPV be mandatory, arguments for and against compulsory immunization with the new human papillomavirus (HPV) vaccine prior to a girl's sexual debut have been raised by ethicist Dr. James Colgrove, Associate Research Scientist, Columbia University, New York.

As Dr. Colgrove noted, the bill proposing compulsory vaccination for girls entering sixth grade (with an option for parents who object to opt out) passed the state senate "by an overwhelming margin" and now awaits consideration by the house. "Other states are likely to follow Michigan's lead," Dr. Colgrove observed, which prompted him to consider arguments supporting mandatory HPV vaccination and those against it.

As he noted, controversy over the vaccine started even before the vaccine was licensed, "when some religious conservatives expressed concern that the availability of a vaccine against a sexually transmitted disease would undermine abstinence-based prevention messages." Conversely, support for compulsory HPV vaccination is likely to be "strongly influenced" by the perception of HPV as a women's health issue. "The severe consequences the disease may have for women lends urgency to the effort to maximize the use of the vaccine through all policy means, including mandates," Dr. Colgrove commented.

Women in Government, an organization of female legislators, is lobbying to make HPV vaccination compulsory in every state. Yet arguments opposing compulsory HPV vaccination are also going to be raised from the public at large who in recent years have shown a growing resistance to vaccination in general, Dr. Colgrove suggested. People may also argue that HPV infection is not as casually transmissible as many other childhood illnesses, so the need for HPV vaccination is less compelling than for protection against measles or pertussis. Programs such as vaccination against hepatitis B have been shown that targeting vaccines to high-risk groups alone are less effective at reducing disease incidence than universal vaccination. "Laws making vaccination compulsory raise unique ethical and policy issues," Dr. Colgrove acknowledged.

Because high levels of herd immunity protect all members of the community—including those who cannot receive vaccines because of medical contraindications—this protection provides a justification for compulsion, Dr. Colgrove postulated. "Requiring HPV vaccination by law will almost certainly achieve more widespread protection against the disease than will policies that rely exclusively on persuasion and education."

The National Advisory Committee on Immunization (NACI) recently issued the following recommendations for use of the quadrivalent vaccine in Canada:

- *Females between 9 and 13 years of age*: The vaccine should be given to girls in this age group, before the onset of sexual intercourse, when its efficacy would be greatest.
- *Females between 14 and 26 years of age*: Females in this age group would benefit from the vaccine, even if they are already sexually active. They may not have been infected with HPV yet and are highly unlikely to have been infected with all four vaccine subtypes. If vaccinated, women in this category need to be aware that they may already be infected with HPV.
- *Females between 14 and 26 years of age who have had previous PAP abnormalities, including cervical cancer, or have had genital warts or known HPV infection*: Sexually active women in this category would still benefit from the vaccine. They may still not have been infected with the HPV types contained in the vaccine and are very unlikely to have been infected with all four vaccine types. If vaccinated, females should not expect the vaccine to have any effect on existing cervical lesions.
- *Immunocompromised persons*: The vaccine can be administered to those who are immunosuppressed as a result of disease or medications; however, its immunogenicity and efficacy might be less than that in those who are immunocompetent.
- *Females >26 years of age and males*: No recommendations at this time. In females >26 years of age, studies are ongoing, although use of the vaccine can be considered in individual circumstances. While immunogenicity data are available for males, the efficacy of the vaccine is still unknown.
- *Females <9 years of age and pregnant women*: Not recommended. Immunogenicity or efficacy is not known in young girls nor is the duration of protection. The data on vaccination in pregnancy are limited and until further information is available, initiation of the vaccine series should be delayed. If a vaccine dose has been administered during pregnancy, there is no indication for any intervention.

Reference:
Canada Communicable Disease Report (CCDR) online publication 15 February 2007;33(ACS-2):1-32. (www.phac-aspc.gc.ca)

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Rotavirus vaccine recommended for all infants in the US with few contraindications

Parashar et al. Prevention of rotavirus gastroenteritis among infants and children. MMWR *2006;55(RR12):1-13.*

According to recommendations from the Advisory Committee on Immunization Practices (ACIP), all infants in the US should receive three doses of the newly licensed rotavirus vaccine at ages two, four and six months unless they have had a serious allergic reaction to any component of the vaccine or to a previous dose of the vaccine.

As of August 2006, the ACIP recommended that infants in the US receive their first dose of the vaccine between the ages of six and 12 weeks, with subsequent doses being given at four- to 10-week intervals. All three doses should be administered by 32 weeks of age. "Rotavirus vaccine can be co-administered with any other childhood vaccines," stated lead author Dr. Umesh Parashar, National Center for Immunization and Respiratory Diseases, Centers for Disease Control, Atlanta, Georgia, "and infants who are being breastfed can receive rotavirus vaccine [as well]."

As Dr. Parashar and colleagues explained, there are several reasons why the ACIP decided to adopt vaccination of infants as the primary public health measure for the prevention of severe rotavirus disease in the US. "First, rates of rotavirus illness among children in industrialized and less-developed countries are similar," they observed, a sign that clean water and good hygiene have little effect on virus transmission and are thus unlikely to prevent rotavirus infection to any significant degree. Furthermore, rotavirus infection continues to be associated with a high level of morbidity even in the US despite the widespread use of oral rehydration solutions. Studies of natural rotavirus infection also indicate that initial infection protects against subsequent severe gastroenteritis. "Therefore, vaccination early in life, which mimics a child's first natural infection… should prevent most cases of severe rotavirus disease and their sequelae," the authors reasoned.

Certain special situations in which infants who do not meet ACIP age criteria for the rotavirus vaccine include premature infants of less than 37 weeks' gestation, for whom the ACIP supports vaccination of this group of infants provided they are at least six weeks of age, are being or have been discharged from the hospital nursery and are clinically stable. The majority of experts also believe that the protection of immunocompromised household members afforded by vaccination of young children in the household outweighs the small risk of transmitting vaccine virus to the immunocompromised household member.

Survey, science rule out association between pervasive developmental disorder and MMR vaccine

Fombonne et al. Pervasive developmental disorders in Montreal, Quebec, Canada: Prevalence and links with immunizations. Pediatrics *2006;118(1):e139-e50.*

D'Souza et al. No evidence of persisting measles virus in peripheral blood mononuclear cells from children with autism spectrum disorder. Pediatrics *2006;118(4):1664-75.*

Katz SL. Has the measles-mumps-rubella vaccine been fully exonerated? Pediatrics *2006;118(4):1744-5.*

An association between pervasive developmental disorder (PDD) and exposure to either high levels of ethylmercury (thimerosal) formerly used in the measles-mumps-rubella (MMR) vaccine or to a one- or two-dose MMR schedule has been categorically ruled out by a large survey of Montreal-based school children born between 1987 and 1998.

Dr. Eric Fombonne, MUHC-McGill University, Montreal, Quebec, and colleagues surveyed 27,749 children born over the 12-year span who were attending 55 anglophone schools at the time. The purpose of the research was twofold: to explore the relationship between trends in PDD rates and cumulative exposure to thimerosal, and to determine if the introduction of a two-dose MMR schedule had any effect on PDD rates.

The survey identified 180 children out of the entire cohort who had a diagnosis of PDD for a prevalence rate of 64.9 per 10,000 children. The largest number of these disorders included autism (21.6 per 10,000), PDD not otherwise specified (32.8 per 10,000) and Asperger's syndrome (10.1 out of 10,000). As researchers noted, the estimate of PDD in this study was "highly consistent" with most recent surveys performed in other countries.

Although PDD rates in this cohort were unexpectedly high, the authors noted that the prevalence rate, which on average increased by 10% a year over the 12 years of the study, was also "consistent" with trends in other studies where increasing PDD rates have been observed in younger birth cohorts over the past 15 years as well.

Researchers pointed out that exposure to thimerosal prior to the age of two for each birth cohort varied over the course of the study from no exposure at all to a high of 225 µg. Consequently, they had a "unique opportunity" to determine whether there was an association between thimerosal exposure and PDD rates. This analysis again revealed absolutely no association between thimerosal levels and PDD rates, the authors reported. Indeed, "it was remarkable that the PDD rates were at their highest value in birth cohorts that were thimerosal-free, providing a clear and convincing message on the lack of an association," researchers stated.

With the introduction of a second dose of the MMR by the age of 18 months, researchers examined the effect of having infants receive a second dose of the vaccine compared to a single dose. Here again, not only was there no association between MMR uptake and PDD rates between 1987 and 1995 when only a single MMR dose was given, but there was again no statistically significant difference between PDD prevalence rates between the years when a single MMR dose was used and following 1996, when a second dose was introduced.

"Therefore, [another] conclusion of this study is that a two-dosing schedule with MMR before [the age of] two years is not associated with an increased risk of PDD," the authors confirmed. As they emphasized in their conclusion, "Parents of children with PDD and the general public should be made aware of the consistency of negative studies on the two hypotheses linking risk of autism and immunization: children with autism and their younger unaffected siblings should be vaccinated."

The same sentiments were echoed by a separate group of researchers under lead author Dr. Yasmin D'Souza, MUHC-McGill University. In this study, investigators sought to determine whether measles virus nucleic acids persisted in peripheral blood mononuclear cells in children with autism spectrum disorder compared with control children. Claims that they persist in tissue and body fluids following MMR vaccination have provided the basis of a hypothesized association between MMR vaccination and autism.

Polymerase chain reaction (PCR) results performed on peripheral blood mononuclear cell samples from 54 children with ASD and 34 developmentally normal children found that no sample from either group contained nucleic acids from any measles virus gene. Furthermore, neither nested PCR results nor in-house assays were able to detect positive results from any of the samples tested and, nor was there any difference in anti-measles antibody titre levels between autism and control groups.

"Our data, together with epidemiologic evidence, demonstrate that arguments against vaccinating children with MMR because of fear of ASD are not defensible on scientific grounds. The risk of death and disability from [measles virus] infection has been unequivocally demonstrated. The hypothesized link between MMR and ASD is spurious and undermines the success of measles control programs," researchers stated.

Commenting on results of this study in the same issue of *Pediatrics*, Dr. Stanley Katz, Duke University Medical Center, Durham, North Carolina, reiterated that independent reviews of all available information regarding MMR vaccination and autism carried out by both the American Academy of Pediatrics and the

Institute of Medicine of the National Academy of Sciences led both groups to conclude that "the available evidence does not support the hypothesis that MMR vaccine causes autism or associated disorders or inflammatory bowel disease." This conclusion was seconded by the Institute of Medicine, which also stated that "the body of epidemiologic evidence favours rejection of a causal relationship between the MMR vaccine and autism."

Efficacy of the 23-valent pneumococcal polysaccharide vaccine in older adults

Vila-Corcoles et al. Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the elderly population: the EVAN-65 study. Clin Infect Dis *2006;43(7):860-8.*

A prospective study evaluating the controversial efficacy of the 23-valent pneumococcal polysaccharide vaccine (PPV) has validated its effectiveness against both pneumococcal pneumonia and mortality due to pneumonia in adults 65 years of age and older.

Dr. Angel Vila-Corcoles, Catalonian Health Institute, Tarragona, Spain, and multicentre colleagues assessed the vaccine's effectiveness in preventing invasive pneumococcal disease (IPD), pneumococcal pneumonia, all-cause pneumonia and death due to pneumonia in elderly citizens living in the community between January 2002 and April 2005. The 23-valent PPV was offered free of charge when elderly subjects visited one of eight primary health care centres in Tarragona, either during the annual influenza vaccination campaign or at any other visit during the remainder of the year.

Some 4986 individuals were vaccinated before the study started, but 87% of them received the 23-valent PPV during the previous two years. Of the 6255 who had not been vaccinated prior to study entry, 23% were vaccinated over the 40-month study period. During the observation interval, IPD was observed in only 22 patients, while community-acquired pneumonia (CAP) was detected in 473 patients, the majority of whom were hospitalized. Based on results from a multivariate analysis, vaccination with the 23-valent PPV was associated with non-significant reductions in the risk of IPD due to vaccine-related serotypes and IPD due to all serotypes, bacteremic pneumococcal pneumonia and non-bacteremic pneumococcal pneumonia.

The vaccine also had a significant protective effect against overall pneumococcal pneumonia, reducing risk by 45% (hazard ratio [HR]: 0.55) as well as the need for hospitalization for pneumonia (26%, HR: 0.74) and overall pneumonia (21%, HR: 0.79). Perhaps most importantly, the risk of death due to pneumonia was 59% lower among vaccinated individuals (HR: 0.41) vs. controls. Investigators acknowledged that the study was not carried out as a randomized controlled study. Still, as they explained, "the large size of our study population, together with adjustment for important covariables in the multivariable analysis, provides an adequate basis for assessing the health effects of pneumococcal vaccination in elderly subjects." They also noted that while the protective effect of the vaccine against IPD did not achieve statistical significance, both crude and adjusted rates of IPD "point to a protective effect against both IPD and bacteremic pneumococcal pneumonia" and noted that their own results mirror those from retrospective studies of pneumococcal vaccination where effectiveness rates range from 60 to 70% in the prevention of IPD.

"In this study, the 23-valent PPV was shown to have a significant efficacy rate… in reducing the risk of hospitalization for all-cause pneumonia and… for the prevention of overall pneumonia," the authors reported. While these two outcome measures are admittedly not as specific as IPD or pneumococcal pneumonia, "they can be used as a good measure of the vaccine's effectiveness." The investigators suggested that the 23-valent PPV should be recommended for all individuals aged 65 years and older, given that it is this age group who are affected most by pneumococcal disease.

School-based influenza vaccine program reduces illness in household members vs. non-intervention schools

King Jr et al. Effectiveness of school-based influenza vaccination. N Engl J Med *2006;355(24):2523-32.*

A school-based influenza vaccination program significantly reduces influenza-related illness in household members compared with control schools which did not offer an influenza vaccine program, despite the fact that fewer than half of the students in schools offering the intervention actually received the vaccine.

Dr. James King, Jr., University of Maryland School of Medicine, Baltimore, and multicentre colleagues assessed the effect of a school-based vaccination program on household members and children attending intervention vs. non-intervention schools. "In the intervention schools, live attenuated influenza vaccine was offered at no charge to all healthy children five years or older in the fall of 2004." Members of households with children in either setting could receive influenza vaccination through their regular health care providers as well. A total of 47% of students in the intervention schools received the vaccine, most of whom had not received it before. During a week of predicted peak influenza activity, all households with children in either the intervention or control schools were surveyed regarding symptoms of flu over the previous seven days.

Results showed that the number of reported episodes of influenza-like symptoms during the peak week surveyed was "significantly lower" in households whose children had attended an intervention school compared with non-intervention control homes. "The use of prescription, over-the-counter and herbal medications for influenza-like illness was [also] significantly lower in households with children in intervention schools than in households with children in control schools, as was the use of humidifiers," investigators added.

Children in intervention-school households also had fewer visits to doctors or clinics for influenza-related symptoms, with a similar trend for adults in the same households, but the difference in emergency room visits was not significantly different between the two groups. Interestingly, members of households whose children attended an intervention school actually had higher hospitalization rates per 100 persons than control households but this difference did not appear to be statistically significant for either children or adults, investigators noted. Importantly as well, absenteeism rates for influenza symptoms in students attending intervention schools were significantly lower than for control students; parents in intervention households also reported significantly fewer lost workdays due to influenza illness.

"Children are important vectors for the spread of influenza within households and communities," the authors concluded, "and focusing efforts for influenza vaccination on healthy children may therefore be an effective and practical method of reducing the burden of influenza in the community."

Hepatitis vaccine schedules for long-term protection

van der Sande et al. Similar long-term vaccine efficacy of two versus three doses of HBV vaccine in early life. Vaccine *2007;25(8):1509-12.*

Rendi-Wagner et al. Persistence of seroprotection 10 years after primary hepatitis A vaccination in an unselected study population. Vaccine *2007;25(5):927-31.*

According to researchers, two doses of hepatitis B vaccine (HBV) protect recipients against long-term core infection and carriage in a highly endemic situation and

may obviate the need for the full three doses. Investigators have also found that protection against hepatitis A following the recommended three-dose schedule persists for over 10 years in an unselected study population.

Dr. Marianne van der Sande, Centre for Infectious Disease Control, Bilthoven, The Netherlands, and colleagues compared HBV efficacy among 60 children who received only two doses of the vaccine as infants to that of 463 other children who received three doses. After four to seven years, the vaccine remained over 86% effective against infection and over 92% effective against carriage among the two-dose group, rates that were similar to those among children who had received three doses. There was no significant difference in geometric mean titres of those who responded between the two-dose and the three-dose groups, nor was there any significant difference between the two groups in terms of serological evidence of previous infection and of ongoing carriage.

"Our observational data support [the possibility] that two doses of HBV vaccination may be enough to protect young children in endemic countries. As both costs and adherence to a vaccination schedule have been shown to have a negative impact on the effectiveness of routine vaccination programs, a shorter schedule could have a significant impact on overall effectiveness," researchers concluded.

In a separate study, Dr. Pamela Rendi-Wagner, Medical University Vienna, Austria, and colleagues assessed long-term immunity and persistence of seroprotection in a large cohort of unselected vaccine recipients 10 years after they had received the primary vaccination course with the hepatitis A vaccine (HAV).

A total of 1016 participants vaccinated with the three-dose HAV schedule, mean age 54.7 years, were included in the study. "Overall, 98.3% of the vaccinees attained protective levels of anti-HAV [equal to or greater than 10 mIU/mL]," investigators reported. Regarding those who achieved anti-HAV antibody titres both above and below 10 mIU/mL, "the only significant result was obtained for body mass index [BMI]," investigators observed, where those with anti-HAV levels of <10 mIU/ml had a BMI of over 31 kg/m^2 compared to the total study population where the BMI was 25.3 kg/ m^2.

Women also achieved higher concentrations of antibody levels than did men, but as the authors concluded, having tested over 1000 individuals, "we observed an overall high seropositivity rate in an unselected population, even in older recipients"—suggesting that after a full course of HAV immunization, "protective immunity exceeds by far the 10-year booster interval currently advised by the manufacturers' prescribing information and most health authorities."

Canadian immigrants, refugees not immune to MMR

Greenaway et al. Susceptibility to measles, mumps, and rubella in newly arrived adult immigrants and refugees.
Ann Intern Med *2007;146(1):20-4.*

According to results of a survey of newly arrived immigrants by Montreal researchers, over one-third of newly arrived immigrants and refugees are not immune to either measles, mumps or rubella (MMR), with women in this group being particularly vulnerable.

Dr. Christina Greenaway, SMBD-Jewish General Hospital, Montreal, Quebec, and colleagues sought to determine the level of susceptibility to MMR among 1480 immigrants and refugees living in Canada for five years or less. Participants had attended one of two hospitals or one of three clinics in the neighbourhood of the Jewish General Hospital between October 2002 and December 2004. "Almost half of the participants were refugees, but only 0.8% had lived in a refugee camp," investigators noted, "and most refugees had applied for asylum after first arriving in Canada."

Of note, participants were well educated, with a mean duration of education approximating 14 years, and almost half had a university education. Serologic results indicated that 36% of the group remained susceptible to at least one of the three infections, with a prevalence ranging from 22 to 54%, depending on age, sex and region of origin. "Immigrant women were especially likely to be susceptible," researchers observed. Results from a multivariable analysis indicated that women were more than twice as likely to be susceptible to measles infection (odds ratio [OR] 2:1) and rubella (OR 1:7) than men but not to mumps.

"Our findings highlight the need to keep MMR vaccinations up to date in foreign-born individuals to protect potentially susceptible persons and to prevent outbreaks," investigators concluded. "More fundamentally, catch-up immunization programs may be necessary and novel strategies that engage immigrant communities and their leaders need to be explored and developed."

Investigators similarly cautioned that susceptible immigrants might unwittingly import MMR on returning from visits with friends or relatives living in areas where the three infections are still endemic. ❑

UPCOMING EVENTS

41st National Immunization Conference
March 5-8, 2007 / Kansas City, Missouri

2007 AMMI Canada-CACMID Annual Conference
March 14-18, 2007 / Halifax, Nova Scotia

2007 World Vaccine Congress
March 19-22, 2007 / Washington, DC

17th European Congress on Clinical Microbiology and Infectious Diseases
March 31-April 3, 2007 / Munich, Germany

National Immunization Awareness Week (Canada)
April 22-28, 2007

4th International Conference on Vaccines for Enteric Diseases
April 25-27, 2007 / Lisbon, Portugal

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