June-July 2008

VACCINE RESOURCE LINE

A MONTHLY SUMMARY OF PEER-REVIEWED PUBLISHED LITERATURE

Clarifying the use of the herpes zoster vaccine

Gnann JW Jr. Vaccination to prevent herpes zoster in older adults. J Pain *2008;9(1 suppl 1):S31-S36.*

The herpes zoster (HZ) vaccine has been approved by the US Food and Drug Administration for prevention of HZ in adults ≥60 years of age, based on the strength of findings from the Shingles Prevention Study (SPS). Nevertheless, there are a number of questions regarding the use of the vaccine, according to Dr. John W. Gnann Jr., University of Alabama, Birmingham, which he set out to clarify in a recent publication.

How long does the protective benefit of the vaccine last?
In the SPS, the efficacy of the vaccine was maintained through four years of follow-up and a long-term follow-up study involving a subset of the SPS population is ongoing. At present, only a single injection of the zoster vaccine is recommended and there is no need for a booster shot at this point in time.

What about its use in patients under the age of 60?
The safety and efficacy of the zoster vaccine in patients under the age of 60 has not been established, although there is no reason to believe that the vaccine would be less safe or less efficacious in younger individuals. Studies of higher-potency zoster vaccines carried out in those ≥50 years of age showed the vaccines were immunogenic and generally well tolerated in participants between 50 and 59 years of age but these studies were not designed to assess efficacy. Given the lack of data, physicians should assess the risk:benefit ratio of off-label use in patients under the age of 60 on a case-by-case basis.

Does the zoster vaccine benefit patients who have already had HZ?
Patients with a prior history of HZ were excluded from the SPS but those who have suffered a previous episode are often the ones who are most insistent on receiving the vaccine. An episode of HZ has an "immunizing" effect and greatly reduces the probability of patients having a second episode. Given this, it is relatively unlikely that someone with an episode in the recent past will benefit from zoster vaccination. However, offering the vaccine to someone with a distant history of shingles (decades ago) is reasonable. The Advisory Committee on Immunization Practices (ACIP) still recommends that adults ≥60 years of age receive the vaccine whether or not they report a prior episode of HZ.

Can the vaccine be used in patients with an unknown chickenpox history?
This question applies to very few adults as at least 95% of adults in North America are positive for varicella. An investigational higher-dose potency zoster vaccine was studied in a small group of adults who were seronegative or who had low titres of varicella antibody, and there were no reports of serious vaccine-related adverse events, no fever and no varicella-like rashes. All of the patients in this group who were seronegative at study outset converted after vaccination. Thus, it is likely that giving the zoster vaccine to varicella-seronegative adults will provide at least partial protection against varicella.

Can the zoster vaccine be given concurrently with other vaccines?
There are limited data to answer this question but at least one study indicated that the zoster vaccine and the influenza vaccine may be given concomitantly without compromising the immunogenicity to either vaccine. There is also no evidence that inactivated vaccines interfere with immune responses to other inactivated vaccines or to live vaccine. Thus, as the ACIP has noted, an inactivated vaccine can be given either simultaneously or at any time before or after a different inactivated vaccine or a live vaccine.

The vaccine is contraindicated in immunocompromised patients. How are we to define this patient group?
The vaccine does contain a live-attenuated strain of varicella, so at least theoretically, it is possible that an immunosuppressed patient could develop a vaccine-associated rash or disseminated infection. The zoster vaccine is clearly contraindicated in patients with lymphoproliferative malignancies, those undergoing cytotoxic chemo- or radiation therapy, organ transplant recipients and HIV-infected patients. But this leaves a large grey zone of mildly to moderately immunocompromised patients in whom the risk vs. the benefit of zoster vaccination is not well defined. The ACIP indicates that the vaccine may be a concern in patients who are receiving more than 2 mg/kg of body weight or 20 mg/day of prednisone (or equivalent) for over two weeks. In contrast, the presence of other medical conditions, including diabetes, is not a contraindication to vaccination, nor is more advanced age.

Can adults be vaccinated if an immunocompromised individual who is varicella-seronegative lives in the same household?
Transmission of vaccine virus after zoster vaccination has not been documented but a theoretical risk exists that it might. The simplest approach here may be to perform varicella serologic testing on the immunocompromised contact and if this contact is seropositive, there is no risk in providing the zoster vaccine to the primary patient, unless the household contact has recently undergone allogenic bone marrow transplantation.

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Most Canadian parents would have their sons vaccinated against HPV

Ogilvie et al. Intention of parents to have male children vaccinated with the HPV vaccine. *Sex Transm Infect* 2008 Apr 29[Epub]

According to a random survey of parents across Canada, over two-thirds of Canadian parents would have their sons vaccinated against human papillomavirus (HPV) in the context of a publicly-funded school-based immunization program.

Dr. Gina Ogilvie, Assistant Professor of Family Practice, University of British Columbia, Vancouver, and colleagues recruited parents of children between the ages of 8 and 18 years through a random digit dialling process. Of 1381 respondents with male children, 67.8% reported that they intended to vaccinate their sons against HPV. "In the same study, 73.8% of parents intend[ed] to vaccinate their daughters against HPV," the authors reported.

As they also noted, intention to have sons receive the HPV vaccine varied across different regions in Canada, from a low of 61.7% in British Columbia to a high of 79.8% in most regions of Atlantic Canada. In multivariate analyses, parents who had a positive attitude towards vaccines in general—and the HPV vaccine in particular—were more likely to intend to have their sons vaccinated against HPV. Parents who reported an intention to have their daughters vaccinated against HPV were also highly likely to report an intention to vaccinate their sons.

Similarly, parents who felt that the HPV vaccine had limited influence on their children's sexual behaviour, as well as parents with more than one child and who were aware of HPV, were more likely to intend to have their sons vaccinated against HPV as well. In contrast, living in British Columbia, as well as a higher educational status, were negatively associated with intention to vaccinate. Religious affiliation, strongly held religious beliefs and cultural background were not significantly associated with intention to have their sons receive the HPV vaccine.

As the authors pointed out, publicly-funded school-based immunization programs for adolescents have achieved good vaccine uptake rates in Canada. For example, uptake rates of hepatitis B vaccine for 12-year-olds of both genders in British Columbia are over 85%.

"Should the HPV vaccine be licensed for boys and men, this study shows that in the context of a school-based vaccine program, the majority of Canadian parents would intend to have their male children receive the HPV vaccine," investigators concluded.

VAERS: women still terminate pregnancy out of vaccine concerns for their fetus

Chang et al. Elective termination of pregnancy after vaccination reported to the Vaccine Adverse Event Reporting System (VAERS): 1990-2006. Vaccine *2008;26(19):2428-32.*

A systematic review of the VAERS (Vaccine Adverse Event Reporting System) database between 1990 and 2006 has revealed that a number of women who inadvertently receive certain vaccines during or shortly before becoming pregnant terminate the pregnancy out of concern that the vaccine may affect the fetus, despite the lack of any evidence to support this concern. Faced with such a situation, health care providers should reassure pregnant women that termination of the pregnancy over vaccine concerns is not necessary.

Dr. Soju Chang, US Food and Drug Administration, and colleagues reviewed reports of elective termination of pregnancy (ETP) in VAERS and sought to describe the circumstances of inadvertent administration of vaccines to pregnant women. "Generally, live-virus vaccines are contraindicated for pregnant women because of the theoretical risk of transmission of the vaccine to the fetus," they observed, "and advisory groups recommend avoiding pregnancy in the immediate period after administration of such contraindicated vaccines."

Between 1990 and 2006, there were 80 reports of an elective termination of pregnancy because of vaccine concerns, most of them from the US. The majority of all of the reports came from vaccine manufacturers. The median age of the women who had elected to terminate the pregnancy was 26. "Of the 80 ETP cases, 73 involved a single vaccine and seven involved multiple vaccines," they noted, while 65 of the 80 reports involved at least one live-virus vaccine, the remaining 15 involving inactivated vaccines only.

Sixty per cent of vaccine recipients were unaware of pregnancy at the time of vaccination while most of the remaining recipients became pregnant within three months of receiving the vaccine. As the authors pointed out, the ACIP recommends women avoid becoming pregnant within one month of receiving a live-attenuated vaccine while manufacturers suggest women avoid becoming pregnant for three months after vaccination.

For their part, the Centers for Disease Control stated that the risk of a developing fetus from vaccination of the mother during pregnancy is primarily theoretical as no evidence exists of such a risk from either inactivated, viral or bacterial vaccine or toxoids. Conversely, live vaccines pose a theoretical risk to the fetus, they added.

"Inadvertent vaccination among pregnant women can be prevented or minimized by enhancing screening and education among women of childbearing potential," investigators stated. "These actions include asking women about pregnancy and date of last menstrual period or intention to become pregnant, and advising women to take precautions to avoid pregnancy within one to three months after live-attenuated vaccine administration."

Hexavalent vaccines highly effective against *H. influenzae* type b disease

Kalies et al. Effectiveness of hexavalent vaccines against invasive Haemophilus influenzae type b disease: Germany's experience after 5 years of licensure. Vaccine *2008;26(20):2545-52.*

A five-year analysis of hexavalent vaccines in Germany indicates the vaccines are highly effective against *H. influenzae* type b disease (Hib) in fully primed as well as fully immunized children.

At the end of 2000, Germany was the first country to introduce hexavalent vaccines by adding a hepatitis B (HBV) component to the previous pentavalent DTaP-IPV/Hib combination vaccine. "To our knowledge, there are no data on field effectiveness of hexavalent vaccines against invasive Hib disease," indicated Dr. Helen Kalies, Ludwig-Maximilians-University, Munich, Germany, and multicentre colleagues. The study therefore estimated the effectiveness of hexavalent vaccines against invasive Hib disease in German children five years after it was introduced.

Surveillance systems showed that 96 cases of invasive *H. influenzae* occurred over a period of five years. Of these, 23 cases were in infants under the age of 2 months, too young to be eligible for vaccination. Of the remaining 73 cases, 32 were type b, 30 non-type b and 11 were not typed. "The clinical diagnosis of all 32 Hib cases was predominantly meningitis," researchers noted, and the median age at diagnosis was 8 months for both unvaccinated and vaccinated children. Of all 13 vaccinated Hib cases, 11 children had received at least one dose of the hexavalent combination vaccine prior to disease onset. "The effectiveness for DTaP-IPV-HBV/Hib combination vaccines against invasive Hib was estimated at 68.4% for an incomplete primary series and 90.4% for the full primary series," the authors reported. "The high effectiveness against Hib for hexavalent vaccines found in this study is

comparable to other DTaP-containing Hib combination vaccines previously reported in Germany."

Combination vaccines have proven to be very useful for public health purposes. They significantly improve the completeness and timeliness of vaccination by reducing the number of injections and doctor's visits in order for children to receive all recommended vaccinations.

Routine pneumococcal conjugate vaccine in childhood reduces pneumococcal meningitis

Tsai et al. Changing epidemiology of pneumococcal meningitis after the introduction of pneumococcal conjugate vaccine in the United States. Clin Infect Dis *2008:46(11):1664-72.*
Smith et al. Alternative strategies for adult pneumococcal polysaccharide vaccination: a cost-effectiveness analysis.
Vaccine *2008;26(11):1420-31.*

Routine childhood vaccination with the pneumococcal conjugate (PCV7) vaccine in the US has dramatically reduced hospitalizations as well as mortality from pneumococcal meningitis in both children and adults to the point where most episodes of pneumococcal meningitis now occur in adults. Dr. Chiaojung Tsai, Vanderbilt University School of Medicine, Nashville, Tennessee, and multicentre colleagues evaluated trends in the incidence and mortality from pneumococcal meningitis hospitalization between 1994 and 2004 using the Nationwide Inpatient Sample, the largest source of inpatient data available in the US. "Overall, pneumococcal meningitis hospitalization rates decreased by 33% after PCV7 introduction," the authors reported.

In children under the age of 2, the average annualized rate of hospitalizations for pneumococcal meningitis dropped by a dramatic 66% since the introduction of the PCV7 vaccine, while there was a 51.5% decrease in annual rates in children between the ages of 2 and 4 years. "During the same period, the rates decreased in older age groups as well," they added, rates among adults ≥65 years of age and older decreasing by 33%. As the authors noted, following routine vaccination with PCV7, the overall mortality rate from pneumococcal meningitis dropped by 32.7%. Children under the age of 2 had the largest decrease in mortality rates (51.1%) but this was closely followed by adults ≥65 years of age, among whom mortality rates from pneumococcal meningitis dropped by 43.9%. Indeed, after the introduction of the vaccine, the authors estimated that there were 3330 fewer hospitalizations for pneumococcal meningitis and 394 fewer deaths compared with baseline years between 1994 and 1999. "Results from this study contribute to the evidence supporting the overall nationwide beneficial effects of PCV7 on pneumococcal meningitis, the most common cause of community-acquired bacterial meningitis," researchers concluded.

In a separate cost analysis of alternative strategies for adult pneumococcal polysaccharide vaccination (PPV), Dr. Kenneth Smith, University of Pittsburgh, Pennsylvania, and colleagues used a model to examine alternative PPV strategies than the currently recommended approach to vaccinate most patients at the age of 65 to prevent invasive pneumococcal disease. The model suggested that providing PPV vaccination to adults at the ages of 50 and 65 would prevent more invasive pneumococcal disease than current vaccination policies and it would not be exceptionally costly to do so. For example, compared to a policy of no vaccination, the present policy costs about $3300 QALY gained. A strategy of vaccinating adults at 50 and 65 years of age would cost about $23,100 QALY gained compared to the present policy. Moreover, researchers found that vaccinating at the age of 65 only—the current policy—was less effective in preventing invasive pneumococcal disease than vaccinating at age 50 only, and that either giving the vaccine at ages 50 and 65 or even at ages 50, 60, 70 and 80 were "reasonable strategies for consideration" and that changes in current PPV recommendations would be "clinically and economically prudent."

Mainstream media has little influence on MMR uptake in the US

Smith et al. Media coverage of the measles-mumps-rubella vaccine and autism controversy and its relationship to MMR immunization rates in the United States.
Pediatrics *2008;121(4):e836-e843.*

According to a report, mainstream media has had surprisingly little influence on uptake of measles-mumps-rubella (MMR) vaccination in the US. Dr. Michael Smith, Children's Hospital of Philadelphia, Pennsylvania, and colleagues aimed to provide for the first time population-level estimates of MMR receipt in the US following publication of a pivotal article in which researchers implicated MMR vaccination and the development of autism. Public-use files of the National Immunization Survey (NIS) were used to estimate annual MMR coverage between 1995 and 2004. "The primary outcome was selective measles-mumps-rubella non-receipt, that is, those children who received all childhood immunizations except MMR," investigators noted.

Media coverage was measured using LexisNexis, a comprehensive database of national and local news media. In 1995, the first year of the NIS, approximately 10% of 19- to 35-month-old children did not receive the MMR vaccine. This decreased to 8% in 1998, then increased again to 10% in 2000 before falling to 7% in 2003 and 2004. Selective MMR non-receipt increased from <1% from 1995 to 1999 to 2.2% in 2000, then returned to baseline over the next two years. As the authors pointed out, an increase in media coverage on the purported link between MMR vaccination and autism began in 2001—well after the observed increase in MMR non-receipt.

Indeed, selective MMR non-receipt had already returned to baseline by the time increased media coverage occurred, suggesting that that parents learned about the MMR-autism controversy from other sources, they speculated. "Even during periods of increased media coverage, attention to the MMR-autism story was short-lived," investigators add. Nevertheless, the increase in both overall and selective MMR non-receipt within the 2000 NIS cohort, of which MMR vaccinations would likely have occurred in close proximity to publication of the index article, was not trivial at a population level, with selective non-receipt of the MMR occurring in approximately one infant in 50 who missed the opportunity for MMR immunizations. Rates were also as high as one infant in 40 attended to in private practice. That physicians may play an important role in MMR delivery is further supported by the finding that neither selective nor overall MMR non-receipt changed significantly in the face of increased media coverage of occurring after 1999, a time when families were more likely to ask physicians about vaccine safety.

"Our findings suggest that physicians may have been an important buffer against the potential negative impact of media coverage of immunization controversies," researchers suggested, "and public health officials must value the provider community as its best opportunity to confront these challenges. Keeping the doctor frequently updated with the most credible information and with strategies for discussing vaccine safety with parents may be the most efficient way to guarantee successful immunization practices in the face of increasing amounts of often unreliable and misleading information."

Needle length, injection site influence risk of local reactions on receipt of the fifth DTaP injection

Jackson et al. Prospective assessment of the effect of needle length and injection site on the risk of local reactions to the fifth diphtheria-tetanus-acellular pertussis vaccination.
Pediatrics *2008;121(3):e646-e652.*

A comparison of needle length along with injection site on the rate of local reactions in children receiving the fifth diphtheria-tetanus-acellular pertussis vaccination (DTaP)

suggests that a 25-mm needle and not a 16-mm needle should be used to decrease local reactions, including pain. If parents want to decrease the risk of redness and swelling at the site of injection, providers should also use the thigh instead of the arm for the same injection.

Dr. Lisa Jackson, Group Health Center for Health Studies, Seattle, Washington, and multicentre colleagues had parents report signs and symptoms of adverse events for seven days after 1315 children between the ages of 4 and 6 received the fifth DTaP injection, 89% of them in the arm and the remainder in the thigh. Two-thirds of the children were vaccinated with a 25-mm needle and one-third were vaccinated with a 16-mm needle. "Among children vaccinated in the arm, the majority reported redness and/or swelling in the vaccinated limb, with 1% to 2% reporting whole-limb redness and/or swelling," study authors noted.

Pain was also reported by more than half of the group who received the injection in the arm and between 16% and 18% reported moderate to severe pain. Moderate to severe irritability or change in activity was reported by <10% of children. Use of a 16-mm needle compared with the 25-mm needle was associated with a significantly higher risk of any redness, 5 cm or greater areas of redness, persistent redness on day 3 and any pain.

Among children vaccinated with the 25-mm needle, vaccination in the thigh was associated with a substantially lower risk of local redness and swelling but with no differences in the risk of pain, irritability or change in activity compared with vaccination in the arm.

"Together, these findings suggest that a 16-mm needle should not be used for administration of the fifth DTaP vaccine injection, and that vaccination in the thigh is an option that may be considered by parents and providers who would like to decrease the risk of local reactions characterized by redness and swelling," researchers concluded.

Hospital-based immunization program against influenza strongly influences pediatric nurses to get vaccinated

Norton et al. Influenza vaccination in paediatric nurses: Cross-sectional study of coverage, refusal, and factors in acceptance. Vaccine *2008;26(23):2942-8.*

An intensive but voluntary hospital-based immunization program against influenza strongly influences pediatric nurses to take advantage of the vaccine, British Columbia researchers reported, and interventions that improve the convenience of hospital-based immunization programs, particularly those aimed at nurses, should be supported.

Dr. Seamus Norton, University of British Columbia, Vancouver, and colleagues examined rates of influenza vaccination among nurses in a pediatric tertiary care centre during an intensive promotional vaccine campaign in which evidence-based strategies to increase coverage were used. "Nearly 76% of eligible nurses were vaccinated in the hospital program, excluding 29 nurses who were vaccinated at an external site," researchers reported. Nineteen nurses had an absolute contraindication to the influenza vaccine and were excluded from the analysis as well. Including nurses vaccinated elsewhere, "the effective coverage rate exceeded 78%," they added. Among nurses who did not take advantage of the influenza program, lack of perceived personal need was the most commonly cited reason overall, being noted by 30% of 258 unvaccinated respondents. Concern about adverse effects or possible harm was the second most common reason. Approximately 39% of nurses who received the vaccine in the hospital program did report at least one post-vaccine symptom, the most common being soreness in the arm for more than one day, which occurred in 60% of vaccine recipients.

Nevertheless, most of the recipients were not deterred by these inconvenient side effects, as 55% of them indicated that they intended to be vaccinated against influenza the following winter. "We found that adequate coverage of nurses in a pediatric centre is achievable during an intensive multi-component program for influenza vaccination using evidence-based strategies," investigators concluded.

Fewer than 30% of healthcare workers at the same centre as well as elsewhere in the province are normally vaccinated against influenza on an annual basis. Up to one-quarter of healthcare workers are infected with influenza each year, and most who develop febrile illness continue to work, leading to increased transmission of influenza to children and other healthcare workers. ❑

UPCOMING EVENTS

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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

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8th Canadian Immunization Conference
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