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Vaccination Against Meningococcal Disease

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(Dr. Pelton was/is the recipient of research grants from, and was/is a consultant for, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, and Wyeth Pharmaceuticals Inc.)

(The author has disclosed that the U.S. Food and Drug Administration has not approved Menveo® or MenHibrix™ for the prevention of meningococcal disease as discussed in this article. As of February 18, 2010, the FDA has not licensed Menveo® for this indication.)

Learning Objective: After participating in this activity, the clinician should be better able to set up universal meningococcal vaccination for adolescents in their practices.

Introduction

Meningococcus deserves our respect. Its reputation for causing rapidly progressive and often fatal sepsis in healthy young adults, despite sophisticated medical care, is well appreciated and has driven the passion for preventive strategies. Yet the demographics of those at risk for meningococcal disease extend from the neonate to the elderly, an important concept to understand as we look at immunization strategies. The peak incidence of disease occurs in the first 6 months of life and is nearly 20-fold greater than the incidence in the general population. However, 17% of cases occur in those between 11 and 19 years of age. Case fatality rates are highest in the elderly and lowest in children and have remained stable at about 11% for the past decade.1

The 4-valent (serogroups A, C, Y, and W-135) meningococcal polysaccharide vaccine (MPSV4; Menomune®) has been licensed since 1981, but its use, until 2000, had been limited to high-risk individuals such as persons with complement deficiencies or asplenia, microbiologists, and military personnel. In the late 1990s, reports of increased cases in late adolescence and among college freshmen living in dormitories2 prompted a reevaluation of preventive strategies. Based on the serogroup distribution in adolescents, it was estimated that 70% of cases were vaccine preventable, and this observation prompted the sequential adoption of a routine vaccination program, beginning with education and voluntary vaccination of college freshmen living in dormitories2 in 2000.3 In 2005, licensure of a 4-valent meningococcal conjugate vaccine that used diphtheria toxoid as the carrier protein (MCV4-D; Menactra®), which had the potential to provide both more durable protection than MPSV4 and a reduction in colonization, led to recommendations for universal immunization of adolescents.4,5 Licensure of MCV4-D was based on non-inferiority with MPSV4 with regard to immunogenicity and safety; no efficacy trials were required by the FDA. Seroconversion rates among adolescents 4 weeks after immunization, based on the development of protective bactericidal titers of ≥1:8, were 92% for serogroup C and 82% for serogroup Y.4

Although vaccine supply was suboptimal during the initial 2 years following licensure, by 2008 more than 40% of adolescents had received MCV4-D (see The Vaccine Quarterly 2009;3[3]:19). The CDC has initiated an ongoing case control study to assess vaccine efficacy.6 Fourteen cases of invasive meningococcal disease were identified in adolescents previously immunized with MCV4-D. Cases were observed in individuals between 12 and 20 years of age and as early as 43 days to nearly 3 years after immunization. Meningitis occurred in 6 of the 14 cases and bacteremia in 8; 3 (21%) cases were fatal. Using vaccine penetration data to calculate the number of immunized adolescents, vaccine efficacy was estimated at 80% to 90% for both serogroup C and serogroup Y.

Is MCV4-D Safe?

In prelicensure trials, MCV4-D was well tolerated and was associated only with local reactions and mild systemic adverse events. After licensure, several cases of Guillain-Barré syndrome (GBS) were identified in adolescents within 42 days of vaccination. Preliminary studies suggested a small increase in GBS cases, estimated at <1 per million doses distributed, and a precaution for adolescents with prior GBS was issued.5 The ACIP reviewed the available data on GBS and MCV4-D in February 2009 and concluded that for individuals 11 to 19 years of age there was no increase in GBS cases above background rates; in the subgroup of those 15 to 19 years of age, the evidence was inconclusive.7 A personal history of GBS remains a precaution (not a contraindication) for use of MCV4-D; for precautions, the default position is not to use the vaccine, although there may be circumstances where the risk is outweighed by the benefit.

Recommendations Revisited

In June 2009, the ACIP revisited its recommendations for MCV4-D.5 The recommendation for immunization of all adolescents 11 to 18 years of age was restated, as well as for immunization of individuals 2 to 55 years of age at high risk for meningococcal disease (complement deficiency, anatomic or functional asplenia, military recruits, entering college freshmen, microbiologists, persons traveling to high-risk areas such as central Africa, and pilgrims to The Hajj). Recommendations were added for subsequent doses in previously immunized persons who remain at increased risk. For persons last vaccinated (with any meningococcal vaccine) at ≥7 years of age, the recommendation was for an additional dose 5 years after the previous one (discussed elsewhere in this issue of The Vaccine Quarterly). For individuals 2 to 6 years of age, revaccination should occur 3 years after the previous dose. Individuals who remain at increased risk (e.g., anatomically asplenic) should be revaccinated every 5 years. The rationale for timing of reimmunization is based on the observation that serum bactericidal activity declines below protective levels more rapidly in younger children than in older children. Re-immunization of entering college students who are or will be living in dormitories was not recommended, unless they were vaccinated more than 5 years previously with MPSV4.
Licensure of another 4-valent meningococcal conjugate vaccine for use in individuals 11 to 55 years of age is expected in early 2010. This vaccine (MCV4-CRM; Menveo®) uses CRM197, a mutant diphtheria toxin, as the carrier protein (CRM197 is also used in PCV7). MCV4-CRM induces higher antibody titers in adolescents than MCV4-D does, but the question remains whether this will translate into clinically meaningful differences in effectiveness and duration of protection (see The Vaccine Quarterly 2009;3[1]:10,13). The immunogenicity of MCV4-CRM may be related to the use of CRM197 itself, which does not have the cross-linking to accessory antigens found in diphtheria toxoid; in addition, the vaccine uses intermediate chain length oligosaccharides that are conjugated to CRM197 in a consistent orientation, factors that may improve immunogenicity.9

Preventing Meningococcal Disease in Infancy

In 2008, an estimated 1,050 cases of meningococcal disease occurred in the U.S., the lowest number of cases in more than 70 years.1,10,11 Previously, the number of cases cycled between 1,800 and 4,800 annually over 5- to 8-year time periods. Whether a fundamental change in disease incidence has occurred, possibly due to the decline in smoking, the use of fluoroquinolones for respiratory tract illness, or other changes in society, or this is simply a delay in the decline in meningococcal carriage, disease, and the impact of serogroup C conjugate vaccination. Am J Epidemiol 2005;162(1):89–100. By permission of Oxford University Press.

 programs for prevention of meningococcal disease. According to one such model, a 2-dose regimen administered at 12 months and 12 years or immunization at 12 months with a catch-up program through 18 years of age results in low rates of disease once vaccine penetration is substantial enough for herd immunity to be present (Figure).11 It remains to be seen if high meningococcal vaccine immunization rates can be achieved among adolescents; until then, direct protection of infants may be necessary. Any way you look at it, in the face of low disease rates (and despite the morbidity and mortality of individual cases), meningococcal vaccination programs have high relative costs per case or death prevented.

The dilemma is likely to be vigorously debated in 2010 once meningococcal conjugate vaccines are licensed for use in infants. For now, the emphasis should be on surveillance to track trends in incidence and serogroup distribution and enhancing efforts to immunize adolescents.

### Table: Invasive Meningococcal Disease in U.S. Infants: 1997–2007

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Serogroup</th>
<th>B</th>
<th>C</th>
<th>Y</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td></td>
<td>27</td>
<td>2</td>
<td>14</td>
<td>3</td>
<td>46</td>
</tr>
<tr>
<td>2 to &lt;4</td>
<td></td>
<td>27</td>
<td>2</td>
<td>13</td>
<td>5</td>
<td>47</td>
</tr>
<tr>
<td>4 to &lt;6</td>
<td></td>
<td>23</td>
<td>8</td>
<td>14</td>
<td>1</td>
<td>46</td>
</tr>
<tr>
<td>6 to &lt;8</td>
<td></td>
<td>25</td>
<td>4</td>
<td>11</td>
<td>2</td>
<td>42</td>
</tr>
<tr>
<td>8 to &lt;10</td>
<td></td>
<td>12</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>18</td>
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<tr>
<td>10 to &lt;12</td>
<td></td>
<td>9</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>123</td>
<td>22</td>
<td>59</td>
<td>11</td>
<td>215</td>
</tr>
</tbody>
</table>


References
Wild animals are the most significant potential source of rabies infection in the U.S. and Canada for both humans and domestic animals. For several decades the majority of human rabies cases have been caused by rabies viruses associated with insectivorous bats, despite the fact that few victims have had documented bat bites. Since the late 1990s, both the ACIP and the Canadian National Advisory Committee on Immunization have recommended rabies post-exposure prophylaxis (RPEP) using rabies vaccine and rabies immune globulin (RIG) when a bat is found in the room of a sleeping person, an unattended child, or an intoxicated or mentally disabled individual, where the possibility of a bite could not be reasonably excluded and where the bat was not available for rabies testing.\textsuperscript{1,2}

This study assesses the practical implications of such broad recommendations using information from a population surveyed in Quebec, Canada. In early 2007, 22,833 households were contacted using random-digit-dialing and asked about bat exposures that had occurred in 2006. Sixty-three percent of households participated, which included 36,445 people. Only 4 people (0.0098\%) recalled significant exposures and none were bitten. Another 152 people (0.43\%) had been in proximity to a bat indoors, with half having either an actual or possible bedroom exposure. Only 2 individuals received RPEP.

<table>
<thead>
<tr>
<th>Contact Scenario</th>
<th>Probability of Rabies\textsuperscript{b} (median (minimum–maximum))</th>
<th>Baseline Cost Scenario\textsuperscript{c} Average Cost-Effectiveness (most cost-effective–least cost-effective)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal tests positive for rabies</td>
<td>(0.01–0.7)</td>
<td>Cost Saving</td>
</tr>
<tr>
<td>Skunk bite\textsuperscript{d}</td>
<td>0.05 (0.01–0.1)</td>
<td>Cost Saving</td>
</tr>
<tr>
<td>Possible bat bite\textsuperscript{d,e}</td>
<td>0.001 (0.000001–0.01)</td>
<td>$2.9 million (Cost saving–$8.4 billion)</td>
</tr>
<tr>
<td>Dog bite\textsuperscript{d}</td>
<td>0.00001 (0.000001–0.001)</td>
<td>$403 million ($524,080–$840 million)</td>
</tr>
<tr>
<td>Dog lick\textsuperscript{d}</td>
<td>0.000001 (0.00000001–0.00001)</td>
<td>$4 billion ($162 million–$840 million)</td>
</tr>
<tr>
<td>Cat bite\textsuperscript{d}</td>
<td>0.001 (0.00001–0.01)</td>
<td>$2.9 million (Cost saving–$840 million)</td>
</tr>
<tr>
<td>Cat lick\textsuperscript{d}</td>
<td>0.000001 (0.00000001–0.00001)</td>
<td>$4 billion ($15 million–$8.4 billion)</td>
</tr>
<tr>
<td>Contact with rabid human in clinical setting\textsuperscript{e}</td>
<td>0.000001 (0.00000001–0.000001)</td>
<td>$4 billion ($162 million–$8.4 billion)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Contact with a potentially rabid animal does not necessarily constitute an exposure. A bite exposure is defined as "any penetration of the skin by teeth." A nonbite exposure is defined as "contamination of open wounds, abrasions (including scratches) or mucous membranes with saliva or other potentially infectious material (e.g., neural tissue)."

\textsuperscript{b} Probabilities of rabies transmission to a human were obtained from a panel of experts, except for "animal tests positive for rabies" when probabilities were obtained from a previous study.

\textsuperscript{c} Estimates of the direct medical costs of rabies postexposure prophylaxis (RPEP) were converted into 2004 dollars using the medical care price index. The cost-effectiveness of RPEP under each contact scenario is calculated using the median probability of becoming clinically ill with rabies and the average cost of RPEP. The most cost-effective ratio is calculated using the minimum cost of RPEP and the maximum probability of becoming clinically ill with rabies. The least cost-effective ratio is calculated using the maximum cost of RPEP and the minimum probability of becoming clinically ill with rabies.

\textsuperscript{d} Animals not available for testing. The skunk bite data are considered applicable to bites from other rabies reservoir species (e.g., bats, raccoons, and foxes in the United States and dog bites occurring in countries with dog variant rabies).

\textsuperscript{e} No recognized bite or saliva exposure.

Based on these findings and the population of Quebec, the investigators estimated that approximately 751 people experienced significant bat exposures (without bites) that year, 53 (7.3%) of whom received RPEP. In addition, approximately 7,548 people had bedroom exposures, with 245 (3.2%) receiving RPEP.

To determine how useful RPEP might be, the investigators calculated the number-needed-to-treat (NNTT) for each case of rabies. This is derived from the absolute risk reduction achieved by administering RPEP. Because there were only 36 known human rabies cases in the U.S. and Canada from 1990 to 2007, and given the combined populations of the countries (5.4 billion person-years), the risk of rabies in the general population is extremely small, which makes the NNTT very high. In fact, the investigators calculated that one would need to treat 59,000 people with direct bat contact (without a bite) in order to prevent a single case of rabies. For bedroom exposures, the NNTT is between 314,000 and 2.7 million people!

They further calculate that RPEP consumes an unreasonable amount of resources. They suggest that for bedroom exposures across the U.S. and Canada each year, 49 physicians, 259 veterinarians, more than 2,000 nurses, and about $1.85 billion ($US) are utilized for investigation, testing, and administration of RPEP. They did not incorporate calculations of serious adverse events from the vaccine, but suggested that this could make the benefits of RPEP even less compelling.

Rabies is a devastating and generally incurable disease, almost universally fatal. In the absence of complete eradication of animal reservoirs, the only reliable preventive action is immediate wound care and RPEP. Even pre-exposure prophylaxis does not provide universal protection.1,3

Both human and domestic animal rabies in the U.S. and Canada have decreased dramatically since World War II, largely due to canine immunization programs and control of unwanted stray animals. Still, in 2006 alone 79 domestic dogs developed rabies, all from contact with wild animals.1 Between 1990 and 2007, 34 human cases of naturally acquired bat-associated rabies were documented in the U.S.; only 8 cases involved a definite or probable bite.1 In 15 cases, no bat bite was documented, though contact did occur (e.g., bat present in home, workplace, or bedroom), and in 11 cases there was no known bat exposure.1

The ACIP charter clearly states that the potential costs and benefits of immunization recommendations are to be considered. RPEP is calculated to be cost-saving for contact with any animal tested and positive for rabies, as well as for bites from a known reservoir animal that cannot be located for testing (skunk, bat, raccoon, fox).1 For a possible or actual bat bite where the animal cannot be located, the average cost is acknowledged to be $2.9 million per life saved (see Table). And yet for ACIP members, this represents an acceptable expenditure given the potential ramifications, confirmed again in the most recent recommendations.1

Between 16,000 and 39,000 people in the U.S. still come into contact with potentially rabid animals annually and receive RPEP based on published recommendations.1,2,4 While the current study questions the utility of these recommendations, there are challenges to making changes in practice based on the calculations from Quebec. Only two-thirds of the population who were contacted actually participated; residents without phones were excluded and the survey depended on recall of exposure only. These things could have affected the accuracy of the assumptions used in these calculations. More importantly, the experience of bat exposure in Quebec may differ from other areas of Canada and the U.S. Previous surveys in Connecticut and Oregon found higher rates of household bat exposures (1% to 1.4% of the population) than were assumed here, and it seems that the bat population increases moving south toward the equator.3 Therefore, changing universal recommendations based on northern data may not apply to other regions.

Still, these issues could affect the cost-benefit calculations in either direction, leaving us still wondering about the benefit of RPEP. The expense of RPEP and recent rabies vaccine shortages have pressed the ACIP to reconsider resource utilization, and newly issued provisional recommendations for RPEP decrease the series from 5 doses to 4 doses.5 Still, until there is a better understanding of the risk factors for acquisition of bat-variant rabies without a bite, providers would be remiss to withhold RPEP in the setting of genuine bat exposures.

—Reviewed by James H. Conway, MD (Please see Dr. Conway’s disclosure on page 2.)

References
Rotavirus has been a common cause of gastroenteritis in developed countries and a common cause of early childhood death in developing countries due to dehydration and subsequent malnutrition. Two live attenuated vaccines against rotavirus, Rotarix®, a 5-valent human–bovine reassortant vaccine (RV5), and Rotarix®, which contains a human G1P[8] strain (RV1), are now available and are considered to have similar efficacy and safety profiles. The ACIP does not express a preference for either RV5 or RV1 (see The Vaccine Quarterly 2008;2[2]:16–17).

This study provides an economic analysis comparing the impact of RV1 and RV5 on the total number of rotavirus gastroenteritis events and associated costs if either were used alone in the U.S. Single-dose uptake of 89%, 2-dose uptake of 79%, and 3-dose uptake (RV5 only) of 70% in a birth cohort of 4.25 million was assumed. The authors employed a societal perspective in the analyses, including items such as caregiver work loss, travel costs for medical care, and costs for extra diapers and oral rehydration solutions. Costs were calculated in 2007 U.S. dollars.

Efficacies of 2 doses of RV1 and 3 doses of RV5 were considered to be identical for deaths, hospitalizations, emergency department visits, outpatient visits, and mild cases requiring no medical attention. Efficacies of 1 dose of RV1 and 2 doses of RV5 were considered to be the same for these outcomes as well. Efficacies of 1 dose of RV5 were assumed to be 50% of those of a single dose of RV1. The cost of RV1 was assumed to be $101.75 per dose and RV5 $68.84 per dose.

The probabilistic modeling process estimated a total vaccine cost for RV5 of $995.4 million, including $126.3 million for vaccine administration, while that of RV1 was $942.9 million, including $84.4 million for vaccine administration. Based on efficacy assumptions, costs (medical plus nonmedical) of rotavirus events not prevented by RV5 were estimated to be $323.8 million, versus $299.1 million for RV1 (8% less than RV5). Estimated societal costs were $1.32 billion for RV5 versus $1.24 billion for RV1. The combination of the costs of rotavirus infection not prevented plus the costs of vaccination was used to determine the net economic benefit of each vaccine. This yielded an estimated cost savings of $77.2 million (95%; 95% CI $71.5 million, $86.5 million), or $18 per child in the birth cohort, over the first 5 years of life if RV1 was used in lieu of RV5.

The authors note that the results were particularly sensitive to the assumed effectiveness of 1 dose of RV1 and the costs of vaccine administration. Sensitivity analyses still favored RV1 over RV5.

We are fortunate to have 2 excellent (efficacious and safe) vaccines against rotavirus infection manufactured by 2 companies (GlaxoSmithKline and Merck) that have a long history of dedication to the development of childhood vaccines. As a general rule, market competition issues aside, we need at least 2 producers of each routine childhood vaccine to ensure adequate supplies over time. Questions that always arise when there are 2 or more products available for vaccination against the same infection are:

(1) Are they really equally effective?
(2) Are they really equally safe?
(3) Are they really equally cost-effective at the societal level?

This study provides an estimated answer to the third question—cost-effectiveness at the societal level. The results suggest that 1 product provides a savings of $18 per child during the first 5 years of life, assuming equal efficacy of full-dose series and “one dose less than full series” of each (2 RV5 doses vs 1 RV1 dose), as well as equal safety. The issue ultimately comes down to assumptions of (1) efficacy of 1 dose of RV1 (for which there are short-term estimates but no definitive published data thus far); (2) vaccine cost per dose for each product; and (3) proportions of the population who receive 1, 2, or 3 doses of rotavirus vaccine.

Most of the economic value assumptions used in this study are reasonably supported by other studies or are neutral in impact. The authors conducted sensitivity analyses of the assumptions that were most vulnerable to bias, with results that still came out in favor of RV1. In the primary analysis, the total cost difference of $18 per child would vanish if the cost per dose of RV5 were reduced by about $7.00. In the least favorable model, dropping the cost of RV5 by about $2.00 per dose would make the societal cost comparison results a “wash.”

One key factor not addressed in the analysis is the impact of herd immunity, which is already apparent at the population level with rotavirus vaccination.1 Herd immunity leads to a net increase in the effectiveness of the vaccines at the population level over that estimated from randomized clinical trials. In the cost analyses used in this study, accounting for an impact of herd immunity would have reduced the estimated difference between the 2 vaccine products in volume of breakthrough disease in partially vaccinated children. This would reduce the apparent difference in medical and societal costs between the products, which in turn would reduce the estimated total cost difference between them.

The origins of this study and my review provide a clear example of the need for transparency. One author of this study is a GlaxoSmithKline employee, and 3 others are employed by Policy Analysis, Inc., which received funding from GlaxoSmithKline for the study. Could this relationship have affected the objectivity of particular assumptions, or the choice of particular references to support such assumptions, that could impact the results of this type of analysis?

On the flip side, you should know my own history. I (as well as the Editor-in-Chief of The Vaccine Quarterly) co-authored (without remuneration) a study on combination vaccines that was conducted in conjunction with GlaxoSmithKline personnel and a similar research group funded by the company.2 In the past, but not during the last 12 months, I (and the Editor-in-Chief) have received honoraria for lectures sponsored by Merck (including the topic of RV5), as well as research support for studies (see full disclosures on page 2). I also have cordial discussions several times a year with science liaisons from both companies. Yet could I be influenced to favor a Merck product and thus pontificate more critically regarding potential biases in assumptions used to generate this cost comparison study?

So, what does one do with the results of this study, as well as this review of it? Take both with a “grain of salt,” “caveat lector,” etc. Remember that both of our vaccine choices for rotavirus are highly safe and effective. Choose what you think will work best in your practice setting. Lastly, be grateful that we have these 2 companies (and a few others) willing to take the financial risks to develop

(continued on page 14)
Learning Objective: After reading this article, the clinician should be better able to manage a patient’s concerns about the efficacy of Hib when used in combination vaccines with DTaP.

Epidemiology of Pertussis and *Haemophilus influenzae* type b Disease in Canada With Exclusive Use of a Diphtheria-Tetanus-Acellular Pertussis-Inactivated Poliovirus-Haemophilus influenzae type b Pediatric Combination Vaccine and an Adolescent-Adult Tetanus-Diphtheria-Acellular Pertussis Vaccine: Implications for Disease Prevention in the United States.

Greenberg DP, Doemland M, Bettinger JA, Scheifele DW, Halperin SA for the IMPACT Investigators; Waters V, Kandola K. 

A combination vaccine containing DTaP, IPV, and Hib (DTaP-IPV/Hib; Pentacel®) was licensed in Canada in May 1997. From 1998 to 2007, it was the only vaccine used in Canada to immunize infants and young children against diphtheria, tetanus, pertussis, polio, and invasive *Haemophilus influenzae* type b disease. The vaccine is administered to children at 2, 4, 6, and 18 months of age, with a DTaP-IPV booster at 4 to 6 years of age.

To determine the impact of this combination vaccine on the incidence and epidemiology of pertussis and invasive *Haemophilus* disease in Canada, the authors searched Medline for publications from 1996 through 2008 related to the epidemiology and vaccine prevention of these two diseases. Related abstracts and presentations were reviewed, when available, and epidemiologic data since 1985 were obtained from the Public Health Agency of Canada (PHAC) public web site.

Reports of pertussis declined substantially in preschool and school-aged children during the 10-year period. For example, between 1998 and 2004 (the last year for which PHAC data were available), the rate of pertussis among children 1 to 4 years of age declined 81.7%. In addition, hospitalizations due to pertussis declined by 85% in this age group (Figure). Furthermore, the usual cyclical peaks in disease incidence that had occurred every 3 to 5 years were blunted or eliminated. In May 1999, a Tdap vaccine (Adacel®) was licensed in Canada for persons 11 to 54 years of age, and in September 2003, recommendations called for universal administration of a single Tdap dose to all adolescents and adults. In provinces and territories where Tdap was administered to 14- to 16-year-olds, marked reductions in pertussis cases were documented in adolescents as well as in younger age groups.

Incidence rates of invasive *Haemophilus* disease among Canadian children <5 years of age declined markedly after introduction of conjugate vaccines in the early 1990s, and the disease remained under control with exclusive use of DTaP-IPV/Hib. Most cases of invasive disease occurred among unimmunized or only partially immunized children. The reduction in *Haemophilus* cases was documented throughout Canada, including among Aboriginal children, who are at high risk for the disease.

The Canadian experience with DTaP-IPV/Hib in infants and Tdap in adolescents is relevant to the United States because both vaccines are licensed for use here, and because immunization schedules, vaccine coverage rates, and epidemiologic patterns of pertussis disease are similar in the 2 countries.

For pertussis, the Canadian experience contrasts with what was seen in the U.S. during this same 10-year period. Here, case numbers of pertussis steadily increased since the 1980s, especially among adolescents and adults.1 In 2004, more than 25,000 cases were reported, representing the highest number of reported cases since 1959. The reasons for the increase in cases were multiple, including waning immunity, greater awareness of the impact of pertussis in teens and adults, and improved diagnostic tests (Canada had also experienced an increase in cases in the late 1980s and early 1990s).2 The Canadian experience reported here offers hope that continued use of acellular pertussis vaccine in infants and widespread use of an acellular pertussis booster in adolescents can lead to improved disease control.

Before licensure of DTaP vaccines in the U.S., combination vaccines containing whole-cell pertussis vaccines and Hib were widely used. Most clinicians anticipated that DTaP-Hib combinations would quickly become the norm. However, candidate DTaP-Hib vaccines from different manufacturers demonstrated decreased antibody responses to the Hib component compared with responses when the vaccines were given separately. Although the clinical relevance of the lower antibody levels was debated,3 these vaccines were not licensed because of concerns that their use could lead to the re-emergence of invasive *Haemophilus* disease. Studies have shown that DTaP-IPV/Hib does not result in lower Hib antibody levels,4 and its success in controlling *Haemophilus* disease in Canada is reassuring.

—Reviewed by Jay M. Lieberman, MD

(Please see Dr. Lieberman’s disclosure on page 2.)

References

This prospective, randomized controlled trial ran from October 1, 2006, to March 31, 2007—long before influenza vaccination was routinely recommended for all children. It was ambitious to run the intervention into spring, given that historically few providers vaccinate against influenza after the New Year’s Eve party leftovers are consumed, despite CDC recommendations. The study involved the first 20 primary care sites from the Children’s Hospital of Philadelphia Pediatric Research Consortium to implement an electronic health record (EHR). Of these, 4 were urban teaching hospital sites (<35% of patients privately insured) and 16 were primarily suburban private practices (>80% privately insured); no practice refused to participate. The 4 teaching hospital sites were randomized to intervention or control separately from the suburban hospitals to ensure a more even distribution of patient characteristics.

All clinicians and interested staff members at both intervention and control sites received education on influenza disease and vaccination. Expert primary care pediatricians delivered a 30-minute presentation and the slides from this were emailed to all clinicians.

Additionally, at intervention sites, the EHR was programmed to alert the health care team of the need for influenza vaccine every time someone opened the record (any visit type) of a “target child,” defined as those between 5 and 19 years of age with asthma and at least one office visit and in need of an influenza vaccine dose at the time of a visit. Having asthma was conservatively defined as having asthma on the chronic problem list or as a diagnosis at any prior visit. The assessment as to whether the child needed a dose included information that tends to be labor-intensive for humans to obtain—history of egg allergy, previous doses, and number of doses needed. The EHR reminder was designed to be noticeable—bold, highlighted, and at the top of the page—and was linked to a vaccine-ordering function.

The outcomes for the intervention and control sites were compared with those for the previous year, after standardization for relevant covariates. The study had >80% power to detect an 8% difference in the change in rates between the study and baseline years at intervention versus control practices.

The study population included 10,667 target children in the baseline year (5,338 control, 5,329 intervention) and 11,919 in the difference in the change in rates between the study and baseline year (vs the previous year, after standardization for relevant covariates; 80% power to detect an 8% difference in the change in rates between the study and baseline years at intervention versus control practices). The outcomes for the intervention and control sites were compared with those for the previous year, after standardization for relevant covariates. The study had >80% power to detect an 8% difference in the change in rates between the study and baseline years at intervention versus control practices.

The study population included 10,667 target children in the baseline year (5,338 control, 5,329 intervention) and 11,919 in the study year (5,809 control, 6,110 intervention). There were no significant differences between control and intervention group characteristics. Notably, only about two-thirds of the patients with asthma who were seen during the baseline year had any visit during influenza season in the study year. After standardization for selected covariates, the proportion of vaccination opportunities that were captured increased 4.2% (from 14.4% to 18.6%) at intervention sites and 3.6% (from 12.7% to 16.3%) at control sites, which was not significantly different. Standardized influenza vaccination rates improved 3.4% more at intervention sites than at control sites, a non-significant difference. In the adjusted analysis, certain factors were significantly associated with improved likelihood of vaccination at a visit:

- Visit for preventive care (vs acute care) (OR 5.33; 95% CI 3.93, 7.24)
- Care at an urban resident teaching practice (OR 2.05; 95% CI 1.62, 2.60)
- Previous receipt of influenza vaccine (OR 1.63; 95% CI 1.36, 2.00)
- Care during the study year (vs baseline year) (OR 1.43; 95% CI 1.30, 1.59)
- Mild intermittent asthma (OR 1.29; 95% CI 1.03, 1.62) or persistent asthma (OR 1.35; 95% CI 1.08, 1.68) on a child’s problem list (vs asthma not on problem list)

Conversely, factors associated with diminished likelihood of vaccination included a visit in January through March (vs earlier), fever, Caucasian (vs African American), 15 to 20 years of age (vs 5 to 9), and female gender. No information was gathered on the reason the vaccine was not given (e.g., provider ignored the alert or parent refused vaccination).

Impact of Electronic Health Record-Based Alerts on Influenza Vaccination for Children With Asthma.
Fiks AG, Hunter KF, Localio AR, Grundmeier RW, Bryant-Stephens T, Luberti AA, Bell LM, Alessandri EA.


Learning Objective: After participating in this activity, the clinician should be better able to assess the limitations of electronic health record alerts in increasing immunization rates.

In 2007, pediatricians in a 4-office, inner-city practice group in Philadelphia led by Dr. Fiks published work showing improved routine immunization rates using provider reminders within the established office EHR.1 As in the current study, the computer system took all the complexities of the routine schedule into consideration, even excluding invalid doses (e.g., doses given at too young of an age or too soon after a previous dose). Not too unlike the system aboard the Starship Enterprise, the computer even suggested which combination vaccines could be used. All this was accomplished with “no perceptible delay in accessing the patient chart.” The alerts, as in the current study, had direct links so the provider could easily order each vaccine. The study demonstrated increases in captured immunization opportunities of 12.1% (from 78.2% to 90.3%) at well-care visits and 20.7% (from 11.3% to 32.0%) at sick visits. When they compared adjusted up-to-date immunization rates at 24 months of age for the control versus intervention periods, they found an increase from 81.7% to 90.1%.

Why weren’t similar improvements achieved using EHR alerts to remind health care providers to give seasonal influenza vaccine to a risk-based target group (children and adolescents with asthma)?

It would be very interesting to learn about the distribution of reasons. What proportion was due to parent refusal, provider error (i.e., stopped noticing the alerts), or active provider decision? The fact that being seen in January through March had the lowest odds ratio (0.18; 95% CI 0.13, 0.25), whereas being seen for well care had the highest (5.33; 95% CI 3.93, 7.24), hints that providers’ understanding of indications and contraindications for this vaccine may be a key to its underutilization. It would be interesting to learn if this study would have had very different results this year—a year in which there are universal recommendations, heightened awareness of pediatric deaths from influenza, and late-arriving vaccine supply.

—Reviewed by Sharon G. Humiston, MD, MPH

Reference
Learning Objective: After reading this article, the clinician should be better able to illustrate increased influenza immunization rates among health care workers.


Guidelines in many countries call for universal vaccination of health care workers (HCWs) against influenza. The prime directive (to borrow a Star Trek term) is to reduce the risk that HCWs will acquire influenza and pass it on to their vulnerable patients. However, influenza vaccination rates among HCWs are universally low. To help design effective immunization programs, the authors reviewed the literature for studies addressing the reasons why HCWs reject or accept influenza vaccination and predictive factors for receiving the vaccine.

This report included 23 studies with information regarding self-reported reasons for rejecting or accepting vaccination among HCWs, gleaned from a PubMed search encompassing the years 1980 to 2008. These studies identified 2 major reasons for suboptimal vaccine uptake: (1) misconceptions or lack of knowledge about influenza infection and influenza vaccines, and (2) lack of convenient access to vaccination. The most common misconceptions or concerns about influenza and the vaccine were fear of adverse reactions from vaccination, lack of concern about the disease, lack of perception of one's own risk, and doubts about vaccine efficacy. Among the studies that named “lack of availability” as a reason, none was from the U.S.

In contrast, among studies reporting on reasons for vaccination acceptance, all but 2 found that HCWs stated self-protection was the most important reason. In the area of “predictive factors for influenza vaccination,” 13 studies were included. At least 5 of them identified the following 3 predictive factors: previous receipt of influenza vaccine, belief in the vaccine’s effectiveness, and older age.

* One of the major precepts in medicine is “Primum non nocere”—“First, do no harm.” One way we can potentially harm our patients is to spread illnesses to them. As a consequence of our jobs, we may be at increased risk of exposure to infections such as influenza. And when we get a runny nose, sore throat, or cough, we usually don’t take a week off from work, in part because of the strong work ethic that we all share. Ironically, it is this ethic in this situation that leads to risk for the very patients we are trying to cure or keep well.

Although annual vaccination is recommended for HCWs to reduce morbidity and mortality associated with influenza in health-care settings, influenza vaccine coverage levels were only 42% among HCWs in the U.S. during the 2005–2006 season and 44% during the 2006–2007 season. Acceptance of influenza vaccination in general has several challenges. Although influenza is a specific viral infection, “the flu” is often used as a generic term to describe a number of respiratory and, incorrectly, gastrointestinal illnesses. Influenza vaccine does not prevent non-influenza illnesses, which leads to the perception that the vaccine doesn’t work (“I got the flu even though I was vaccinated.”) or that the vaccine caused the illness (“I got the flu from the vaccine!”). Furthermore, the vaccine is not 100% protective and its effectiveness may be much lower in years when the vaccine strains are poorly matched to the circulating strains; therefore, some people actually do get influenza despite vaccination. Finally, the need for annual vaccination makes compliance more challenging.

This paper was particularly timely given all the hoopla about pandemic H1N1 influenza (see Editor’s Section elsewhere in this issue). Influenza vaccination of HCWs was in the news because hospitals and some states made or tried to make vaccination mandatory. This paper’s findings indicate that if HCWs get immunized against influenza, they do so primarily for their own benefit and not for the benefit of their patients. Quite frankly, I don’t care why people get vaccinated as long as they do. As Captain Jean-Luc Picard from Star Trek would say, “Make it so!” Influenza vaccines are not perfect, but they offer the best opportunity to protect our patients and ourselves from a potentially serious infection. We need to increase educational efforts so that HCWs (and others) understand the truth about the safety and effectiveness of influenza vaccines. And HCWs should recognize their ethical responsibility to help protect their patients against influenza and other health-care associated infections.

—Reviewed by Jay M. Lieberman, MD

Reference

A combination vaccine against measles, mumps, rubella, and varicella (ProQuad®) was licensed in 2005. Although most of the side effects observed in pre-licensure trials were similar to those seen in children who received separate MMR (M-M-R®II) and VAR (Varivax®) injections, MMRV recipients were noted to have fever and rash more frequently.1

This collaborative observational study between Merck Research Labs and Kaiser Permanente Southern California (KPSC) was designed to assess the safety of MMRV in a larger population after it became available for general use. The primary intent was to compare the incidence of febrile convulsions after administration of MMRV with the incidence previously seen with separate MMR and VAR (MMR+VAR) injections given simultaneously.

The KPSC system represents a largely self-contained health maintenance organization (HMO) with more than 3.2 million members. Nearly all children in this HMO receive their routine care (including vaccinations) and acute care in affiliated facilities; thus, the data available are comprehensive. The study population included 31,298 children 12 to 60 months of age (99% were 12 to 23 months) who received MMRV from February 2006 to June 2007, who had never before received vaccines containing any of these components, and whose disease had not been documented. A historical comparison cohort of 31,298 subjects was chosen from children immunized with MMR+VAR between November 2003 and January 2006. The 2 groups had similar demographic characteristics.

Potential convulsions were identified from health encounter and claims records where any type of diagnostic code suggesting seizure activity was used, regardless of the setting (inpatient, outpatient, or urgent care). An adjudication panel then reviewed de-identified records from each episode to determine whether it fit the strict Brighton Collaboration criteria for a febrile convulsion.2 The investigators were primarily interested in events occurring 5 to 12 days post-immunization, but collected data through day 30 as well. To assess the background rate of seizures in this population, the investigators also collected convulsion data from the MMRV recipients for a month before and after the study period.

Of the 370 possible convulsion events recorded for the 62,596 children, one-third were excluded due to incomplete records or follow-up, and another third were adjudicated to not be febrile convulsions. Of the remaining 123 cases, a third occurred outside the 30-day period of interest. This left 44 confirmed febrile convulsions over days 0 to 30 in the MMRV group (incidence rate [IR] 1.41 per 1000), and 40 in the MMR+VAR comparison population (IR 1.28 per 1000), which is not a statistically significant difference.

The difference of note occurred in days 5 to 12 after immunization, where 22 children experienced febrile convulsions after MMRV (IR 0.70 per 1000) compared with only 10 after MMR+VAR (IR 0.32 per 1000). In other words, febrile convulsions 5 to 12 days post-vaccination were twice as likely after MMRV compared with MMR+VAR. In terms of patients affected, this amounts to 1 additional febrile convulsion per 2,600 children vaccinated.

There are a number of limitations to this study, acknowledged by the authors. Most important is the fact that the MMRV recipients received significantly more vaccines on the same day, including HepA and PCV7, than the historical controls.

References
Learning Objective: After participating in this activity, the clinician should be better able to apply educational interventions that increase postpartum pertussis immunization rates.

Pertussis Immunization in a High-Risk Postpartum Population.
Healy CM, Rench MA, Castagnini LA, Baker CJ.

Reported rates of pertussis increased in the U.S. in the early 2000s despite high rates of vaccine coverage among young children. Cases rose disproportionately among adolescents and young adults. Cases in infants also increased, and 75% of the time the disease was acquired from a household contact, often the mother. The main reason that pertussis continues to circulate among adolescents and adults is that vaccine-induced immunity (and natural immunity, for that matter) wanes within 5 to 8 years. With the advent of Tdap booster vaccines, targeted immunization of adolescents and adults was recommended as a way of surrounding infants too young to be vaccinated in a “cocoon” of immunity.1,2 The cocooning strategy includes giving Tdap to postpartum mothers before hospital discharge, as well as immunizing all household adolescents and adults. Postpartum vaccination is a new approach with little established infrastructure to ensure effective implementation.

This study evaluated the impact of educational efforts targeting healthcare providers plus standing orders to offer Tdap to postpartum women in a public hospital in Houston, Texas. The population was >90% Hispanic and predominately Spanish-speaking. Physicians were informed about the prevention strategy in obstetrical service grand rounds. Small group in-service sessions were conducted for physicians, nurses, interpreters, and administrative staff. Information leaflets were provided to postpartum women. Women who consented to vaccination received Tdap on the day of hospital discharge in order to avoid concerns that any fever after vaccination might lead to unnecessary evaluations. Individuals with self-reported contraindications to vaccination or after vaccination might lead to unnecessary evaluations.

From January 7 to April 20, 2008, 1,129 of 1,570 (72%) postpartum women received Tdap before discharge. The median age was 26 years (range 13–46). Tdap uptake among eligible women was 96%. Reasons for not being vaccinated (441 women) are shown in the Figure. In 7%, the vaccine was not ordered. One-third of women who reported recent tetanus immunization had actually received other vaccines, most often influenza vaccine. Among 45 women who refused vaccination, the reasons for refusal included history of local reactions to vaccines, intercurrent illness, medical conditions that were not true contraindications, religious objections, and uncertainty about past receipt of Tdap. The small subset of African-American women (n = 95) in the study group were more likely to refuse vaccination for non-medical reasons (24% vs 9%, P = 0.003). No serious adverse events related to vaccination were reported.

*This study demonstrates the effectiveness of provider education plus standing orders as a means of initiating a postpartum Tdap vaccination program in a public hospital, where physicians and staff are arguably more overburdened than in private settings. The uptake by eligible mothers in this largely Hispanic, predominately Spanish-speaking population was an outstanding 96%. The study provides no data as to which component played a more important role—the

standing order or provider education—but it is easy to conclude that one without the other would have had less spectacular results. Periodic re-education and in-servicing of physicians, nurses, and staff likely will be essential to maintain this level of success.

A focus on the cocoon into which newborns enter will be required until cohorts of women reach the childbearing years already having received routine Tdap boosters as adolescents, or at least until there are vast improvements in offering Tdap boosters to young adults during health care visits. The good news is that Tdap coverage among adolescents has increased to 40.8%, an all-time high (see The Vaccine Quarterly 2009;3[3]:19). The bad news is that in 2007 only 2% of adults had received a Tdap booster in the prior 2 years. Thus, it likely will be many years before population-level immunity to pertussis among women of childbearing age reaches the level where postpartum immunization may become unnecessary.

Unless administration of Tdap during the second or third trimester of pregnancy becomes routinely recommended down the road, the “postpartum immunization platform” (terminology of the authors) will remain a key health care contact point. Counseling regarding the postpartum dose and the need to have other close contacts immunized should become part of prenatal care programs.

The standing order system used in this study did fail in a few cases. This may be a result of the specific format used, and this was not specified in the article. Standing orders that can be implemented by nursing staff likely will be more “failsafe” than standard order sets that require a physician to check a box to authorize an order before it is implemented. The former should provide detailed instructions to (1) review specific vaccine contraindications and precautions; (2) offer vaccination in the context of a Vaccine Information Statement-based consent process if there are no contraindications; (3) document any reason given for refusal; and (4) notify the attending physician of patient refusal. The latter hopefully would trigger further discussion of the issue between the patient and the physician.

Learning Objective: After participating in this activity, the clinician should be better able to interpret the risks of HPV vaccination for their patients.

Postlicensure Safety Surveillance for Quadrivalent Human Papillomavirus Recombinant Vaccine.

The FDA licensed the 4-valent human papillomavirus vaccine (Gardasil®; HPV4) in June 2006, and shortly thereafter the ACIP recommended routine vaccination of adolescent females. By the close of 2008, more than 23 million doses had been distributed in the U.S. The study reviewed here details adverse events following immunization (AEFIs) with HPV4 that were reported to VAERS during the post-licensure period. Although vaccine safety was evaluated in pre-licensure studies, the number of individuals in those studies was much smaller than the population of vaccine recipients represented in this study.

VAERS is a collaborative effort by the CDC and FDA (for more information, see http://www.vaers.hhs.gov). Its goal is to detect patterns in AEFI reports that would reveal a potential problem with a vaccine, in essence generating a signal that something may be wrong. This would then prompt population-based research (VAERS is not population-based because it only includes patients with potential AEFIs) to look for a true association between the vaccine and the event. VAERS encourages reporting from anyone who thinks that they (or their child, patient, or law practice client) may have had an AEFI. Personnel at both the FDA and CDC review all reports. Because the reports are voluntary and not systematic, many AEFIs go unreported. Conversely, a VAERS report does not indicate that the health problem was caused by vaccination, only that the event followed vaccination.

During the study period, VAERS received 12,424 reports of AEFIs following HPV4, a rate of 53.9 reports per 100,000 doses distributed. Table 1 shows the distribution of non-serious and serious AEFIs, including the total number of events that occurred after vaccination with HPV4 alone. Just above 6% of reported events were described as serious (i.e., life-threatening or resulting in death, permanent disability, a congenital anomaly, hospitalization, or prolongation of hospitalization). Among the 32 deaths reported, the mean

<table>
<thead>
<tr>
<th>AEFIsa</th>
<th>Number of Events</th>
<th>Reporting Ratec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope, syncope vasovagal</td>
<td>93 (5%)</td>
<td>8.2</td>
</tr>
<tr>
<td>Local reaction</td>
<td>41 (2%)</td>
<td>7.5</td>
</tr>
<tr>
<td>Dizziness</td>
<td>96 (6%)</td>
<td>6.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>119 (10%)</td>
<td>5.0</td>
</tr>
<tr>
<td>Headache</td>
<td>150 (16%)</td>
<td>4.1</td>
</tr>
<tr>
<td>Hypersensitivity reaction</td>
<td>47 (6%)</td>
<td>3.1</td>
</tr>
<tr>
<td>Urticaria</td>
<td>22 (4%)</td>
<td>2.6</td>
</tr>
<tr>
<td>Venous thromboembolic event</td>
<td>39 (69%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Autoimmune disorder</td>
<td>19 (37%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>31 (74%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>8 (29%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Death</td>
<td>32 (100%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Transverse myelitis</td>
<td>10 (100%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>9 (100%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Motor neuron disease</td>
<td>2 (100%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

aUsing MedDRA terms. More than 1 code may be assigned to a single report.

bNo other vaccine was coadministered.

cReports per 100,000 doses distributed.

dLocal injection site reaction MedDRA codes include injection site abscess, injection site abscess sterile, injection site atrophy, injection site cyst, injection site desquamation, injection site hemorrhage, injection site hypersensitivity, injection site inflammation, injection site mass, injection site necrosis, injection site nodule, injection site edema, and injection site pain.

eHypersensitivity reaction MedDRA codes include anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, cross-sensitivity reaction, dermatophagism, hypersensitivity, urticaria, urticaria thermal, and urticaria vesicular.

time from the last HPV4 vaccination to event onset was 39 days (median 14.5 days, range 2–288 days). Analysis of the deaths revealed no common pattern; rather, when an autopsy, death certificate, or medical record was available, the cause of death was most often related to diabetes, viral illness, illicit drug use, and heart failure. However, 2 deaths were reported in young females from an unusual neurological illness (probable variants of amyotrophic lateral sclerosis).

Statistical methods were used to detect disproportionality in reporting. While most of the AEFI rates were not greater than background rates compared with other vaccines, syncope and venous thromboembolic events (VTEs) were disproportionally reported.

In 10% of the reports of syncope with a known onset interval, the event did not occur on the day of vaccination. When syncope occurred on the day of vaccination and a more specific time frame was given, >50% occurred within 15 minutes of vaccination. Among the 1,896 syncope events, 293 (15%) resulted in a fall and 200 of these falls (68%) resulted in head injuries of varying severity (5 intracranial hemorrhages, 9 fractures, 18 dental injuries, and 38 lacerations requiring sutures). This signal led the CDC and FDA to encourage clinicians to carefully watch vaccine recipients for 15 minutes after vaccination.1

The reports of VTEs do not lead to a clear conclusion. There were 56 such reports—10 by hearsay, 9 discovered not to be VTEs (they were “clots with menses”), 6 without adequate information, and 31 that were appropriate for clinical review. Of these 31, 28 females (90%) had a known risk factor for VTEs. Nonetheless, close monitoring continues for VTE reports following HPV4 as well as other vaccines.

In summary, the findings were similar to the safety reviews of meningococcal vaccine and Tdap, also recommended for adolescents and young adults. The FDA and CDC continue to consider HPV4 to be safe, with risks that are far outweighed by the benefits.

Despite (or, arguably, because of) the media controversy surrounding HPV4, a sizable number of adolescent females have received the vaccine. The proportion of girls 13 to 17 years of age who, in 2008, reported having received ≥1 dose of HPV4 varied by ethnicity and household income,2 while the proportion receiving ≥3 doses of HPV4 was considerably lower (Table 2). The size of the cohort receiving the vaccine makes the importance of its safety even more acute.

The federal commitment to vaccine safety is considerable. The CDC and collaborating scientists are following up on the 2 neurological deaths after HPV4 vaccination. The Vaccine Safety Datalink, an active surveillance system, has been using real-time methods looking for multiple AEFIs, including blood clots and pulmonary emboli, but to date has not detected an elevated risk following HPV4. Additionally, both the CDC and FDA are undertaking studies on the disproportional VAERS reporting for syncope.

While studies evaluate the long-term effectiveness and impact of vaccination against HPV, clinicians who have to decide whether to recommend vaccination can be fortified by the knowledge that—at the very least—HPV4 is safe.

—Reviewed by Sharon G. Humiston, MD, MPH

References

Cost of Routine Immunization of Young Children Against Rotavirus Infection With Rotarix Versus RotaTeq (continued from page 7)

vaccines that improve the quality of life of children in this country and other developed nations and that save the lives of many children around the world every day.

—Reviewed by Charles R. Woods, MD, MS

(please see Dr. Woods’s disclosure on page 2.)

References

Observational Safety Study of Febrile Convulsion Following First Dose MMRV Vaccination in a Managed Care Setting (continued from page 11)


Table 2. Estimated HPV4 Coverage Among Adolescent Girls 13–17 Years of Age in 2008

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>≥1 dose of HPV4</th>
<th>≥3 doses of HPV4</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>35.0%</td>
<td>19.5%</td>
</tr>
<tr>
<td>African-American</td>
<td>35.7%</td>
<td>14.9%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>44.4%</td>
<td>14.7%</td>
</tr>
<tr>
<td>Household income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below poverty level</td>
<td>46.4%</td>
<td>14.9%</td>
</tr>
<tr>
<td>Above poverty level</td>
<td>35.8%</td>
<td>18.6%</td>
</tr>
</tbody>
</table>


Pertussis Immunization in a High-Risk Postpartum Population (continued from page 12)

Two final points made by the authors merit mention. First, the history of prior receipt of Tdap vaccine was erroneous in one-third of the women who gave it. The primary source of confusion was prior receipt of another vaccine, usually influenza vaccine. This underscores the importance of ready access to health records of all types, or at least vaccine registries for adults as well as children. Second, the rate of Tdap refusal was higher among African-American women. The authors note that higher vaccine refusal rates have been noted among African-American adults in other studies. This suggests that educational materials need to be culturally sensitive and tuned in to issues particular to certain demographic groups.

—Reviewed by Charles R. Woods, MD, MS

References
2009 INFLUENZA H1N1 UPDATE

Here is where we stand in the U.S. on the 2009 H1N1 influenza pandemic at the time of this writing (November 30, 2009):4

- Almost all cases identified this season have been caused by the novel 2009 H1N1 influenza A virus. Isolates remain similar to the seed virus chosen for the vaccine, and they remain susceptible to oseltamivir and zanamivir.
- Influenza activity remains high for this time of year but is beginning to decline in most parts of the country. Visits to doctors for influenza-like illness declined during the month of November after 4 straight weeks of increases. Hospitalization rates and deaths attributed to influenza and pneumonia have also begun to decline. Questions remain as to whether there will be additional waves of 2009 H1N1 illness this winter and spring and whether seasonal influenza viruses will reappear.
- The CDC estimates that 22 million cases occurred between April and October 2009, resulting in 98,000 hospitalizations and almost 4,000 deaths.5 The majority of cases (~12 million), hospitalizations (~53,000), and deaths (~3,000) have occurred among individuals 18 to 64 years of age. To date, nearly 200 pediatric deaths have been attributed to the 2009 H1N1 influenza virus, which exceeds the number of pediatric deaths that are usually reported as a result of seasonal influenza each year. The demographics of those most affected by this disease continue to be markedly different from seasonal influenza, which primarily affects those 65 years of age and older.

As of the end of November, 52 million doses of 2009 H1N1 influenza vaccine have been shipped.3 These doses are 1 of 3 available forms of IIV-2009 H1N1* (made by CSL Biotherapies, Novartis, and sanofi pasteur) and 1 form of LAIV-2009 H1N1* (made by MedImmune) (see The Vaccine Quarterly 2009;3[3]:16). On November 16, a fourth IIV-2009 H1N1 product, manufactured by ID Biomedical Corporation of Quebec and distributed by GlaxoSmithKline, was licensed by the FDA. Licensure was granted based on immunogenicity studies of the analogous seasonal vaccine, FluLaval® (the same egg-based process is used to make both vaccines). The vaccine is indicated for individuals ≥18 years of age and is supplied in 10-ml multidose vials (each dose is 0.5 mL) containing thimerosal as preservative (25 mcg mercury per dose).

Use of one particular lot (GlaxoSmithKline A80CA007A) of IIV-2009 H1N1 in Canada was suspended because of severe allergic reactions that were reported at a rate 5 times higher than expected; this vaccine was not distributed in the U.S. Intensive safety monitoring continues here (see The Vaccine Quarterly 2009;3[3]:17). Between October 1 and November 24, VAERS received 3,783 reports of adverse events after receipt of 2009 H1N1 influenza vaccine.7 This amounts to 82 reports per million doses distributed (4.4 serious reports per million), which is higher than the 47 per million (2.9 serious reports per million) reported after seasonal vaccine. However, no unique pattern of adverse events was seen for 2009 H1N1 vaccine, and the proportion of events that were serious was higher for seasonal vaccine than for 2009 H1N1 vaccine (6.1% vs 5.4%). It is possible that the increase in reports seen after 2009 H1N1 vaccine is the result of deliberate efforts to enhance reporting as well as heightened public awareness (remember, VAERS is a passive reporting system tracking events that follow vaccination that may or may not be causally linked to vaccination).

There were 13 reported deaths. In 9, there were serious underlying illnesses; 1 death resulted from a motor vehicle accident and 3 were awaiting confirmation.4 Preliminary investigation showed no common cause of death in these cases. VAERS also received reports of 10 cases of Guillain-Barré syndrome (GBS), and 2 additional possible cases were found upon review of other neurological events (GBS was seen with increased frequency after the swine influenza vaccine was widely distributed in 1976 [see The Vaccine Quarterly 2009;3(2):17–19]). Four cases met Brighton Collaboration5 criteria for GBS, 4 did not meet the criteria, and 4 are under further review. These reports, even if confirmed, do not raise any red flags, as 80 to 160 cases of GBS are expected to occur each week in the U.S., regardless of vaccination. There were also 19 possible cases of anaphylaxis, 13 of which met Brighton Collaboration criteria. Importantly, the Vaccine Safety Datalink revealed no cases of GBS and only 1 case of anaphylaxis among nearly half-a-million vaccinees, and there was no increase in other monitored conditions after vaccination.8

Many communities have undertaken mass immunization campaigns, the likes of which have not been seen since the Salk vaccine was rolled out in the mid-1950s. Although not without snags, the overall effort has been extremely successful. The view from 10,000 feet is nothing short of remarkable. The first cases of this novel, never-before-seen influenza virus were detected in April 2009. Seven months later, tens of millions of doses of vaccine had been manufactured, distributed, and given to people, the vast majority of whom would have been defenseless without it.

References


* These abbreviations for influenza vaccines were introduced in the last issue of The Vaccine Quarterly. “Trivalent Inactivated Vaccine” (TIV) has been replaced with “Inactivated Influenza Vaccine, Seasonal 3-Valent” (IIV-seasonal). This more accurately differentiates the seasonal vaccine from the monovalent 2009 pandemic vaccine, “Inactivated Influenza Vaccine, 2009 H1N1, monovalent” (IIV-2009 H1N1). The reasoning behind “LAIV-seasonal” and “LAIV-2009 H1N1” is similar.
Until October 2009, only 3 of the available seasonal influenza vaccines in the U.S. were labeled for use in children: Fluzone® (IIV-seasonal, sanofi pasteur), ≥6 months of age; Fluvirin® (IIV-seasonal, Novartis), ≥4 years of age; and FluMist® (LAIV-seasonal, MedImmune), 2 to 49 years of age (see The Vaccine Quarterly 2009;3[3]:16). That month, the FDA extended the age indication for Fluarix® (IIV-seasonal, GlaxoSmithKline) to include individuals ≥3 years of age, adding one more option for kids and technically filling a gap that had existed for 3-year-olds, who formerly only had one IIV-seasonal option (Fluzone®). The vaccine is formulated without preservatives and is supplied in 0.5-mL single-dose prefilled syringes (the tip cap and plunger of these syringes contain latex and may cause allergic reactions in latex-sensitive individuals).

In an immunogenicity study involving several hundred children 3 and 4 years of age, Fluarix® met at least one pre-specified non-inferiority criterion for influenza A when compared with Fluzone® (non-inferiority criteria were not met for influenza B). However, seroconversion rates to the influenza A strains (~70%) and influenza B strain (~55%) were similar for the 2 vaccines, as were the proportion of children achieving protective antibody titers (82%–94% for influenza A and 55%–58% for influenza B). The most common adverse events were pain, redness, and swelling at the injection site, irritability, loss of appetite, and drowsiness. The proportion of subjects 3 to 17 years of age with solicited adverse events within 4 days of vaccination was similar to that seen with the comparator vaccine.

The ACIP is silent on the use in 3-year-olds of the other brands of IIV-seasonal that are licensed for individuals ≥4 years of age, although there are other situations where vaccines are used off-label (for example, revaccination with MCV4 is recommended in certain situations, even though the vaccine is only labeled for 1 dose; see below). The risk of doing so seems minimal, and almost certainly outweighs the risks associated with letting a 3-year-old go unvaccinated.

(The author has disclosed that the U.S. Food and Drug Administration has not approved some brands of IIV-seasonal for the treatment of influenza in 3-year-old children in the manner discussed here. Please consult the product labeling information for approved indications and usage.)

Reference

### AGRIFLU® LICENSED

In November 2009, the FDA added another trivalent, inactivated seasonal influenza vaccine to the ones already available in the U.S. (see The Vaccine Quarterly 2009;3[3]:16). Agriflu®, manufactured by Novartis (which already distributes Fluvirin® in the U.S.), is indicated in persons ≥18 years of age. It is an egg-based vaccine that is formulated without adjuvant or preservatives. Each 0.5 mL dose may contain residual egg proteins, formaldehyde, polysorbate 80, neomycin, kanamycin, and cetyltrimethylammonium bromide. Licensure was based on immunogenicity (seroconversion and proportion of subjects with hemagglutination-inhibition titers ≥1:40) that was non-inferior to a licensed vaccine. Agriflu® is supplied in 0.5-mL single-dose prefilled syringes (the syringes do not contain latex).

Reference

### SEASONAL INFLUENZA VACCINE COVERAGE RATES

Annual influenza vaccination has been recommended for all children 6 to 23 months of age since 2004, all children 24 to 59 months of age since 2006, and all children and adolescents 5 to 18 years of age since 2008. The CDC recently published estimates of coverage among individuals 6 months to 18 years of age for the 2008–2009 season, derived from 8 immunization information system (IIS, formerly referred to as registry) sentinel sites with a collective enrollment of more than 5 million children. In general, coverage rates decreased with age, in part reflecting the newness of the universal recommendation for children over 5 years of age (Table 1). However, there is no excuse for a full vaccination coverage rate of only 28.9% among young infants and toddlers. Full vaccination for the 2009–2010 season will mean 4 shots for most of these kids (2 IIV-seasonal and 2 IIV-2009 H1N1), so the sooner we get in gear, the better!

Figures similar to those above were generated from an analysis of data from the Behavioral Risk Factor Surveillance System. That study also looked at influenza coverage among adults. Unfortunately, coverage for persons 18 to 49 years of age with high-risk conditions was only 32.1%. Coverage was 42.3% for adults 50 to 64 years of age and 67.2% for those ≥65 years of age. These rates represented no gains over previous years.

### Table 1. Seasonal Influenza Vaccine Coverage Rates, 2008–2009 Season

<table>
<thead>
<tr>
<th>Age group</th>
<th>≥1 dose</th>
<th>Full vaccinationa</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–23 months</td>
<td>47.8%</td>
<td>28.9%</td>
</tr>
<tr>
<td>2–4 years</td>
<td>27.8%</td>
<td>21.8%</td>
</tr>
<tr>
<td>5–10 years</td>
<td>16.3%</td>
<td>12.0%</td>
</tr>
<tr>
<td>11–12 years</td>
<td>12.7%</td>
<td>—</td>
</tr>
<tr>
<td>13–18 years</td>
<td>9.1%</td>
<td>—</td>
</tr>
</tbody>
</table>

aFor children 6 months to 8 years of age who had never been vaccinated before or who received only 1 dose when first vaccinated in the previous season, full vaccination was defined as receipt of 2 doses ≥4 weeks apart in the current season. For all other children, full vaccination was defined as receipt of 1 dose in the current season.

Adapted from Centers for Disease Control and Prevention. MMWR 2009;58:1059–1062.

### References
In October 2009, Merck announced that it would no longer manufacture the separate monovalent vaccines. Many reasons were cited, including the following:

- MMR is preferred over the separate vaccines by authoritative bodies such as the ACIP, AAP, and AAFP.
- MMR eliminates the risk of delayed protection caused by separating out the vaccinations.
- There is no medical reason to deliver the vaccines separately—doing so, in fact, increases risk but provides absolutely no benefit.

This decision, which was made after intensive deliberation and input from the ACIP, professional societies, scientific leaders, and customers, will have a net positive public health impact.

References
of reactions was similar in both groups. There were 18 deaths in vaccinees and 19 in placebos, and the causes of death were the expected events in healthy adolescent and adult age groups, such as motor vehicle accidents, drug overdoses, suicides, gunshot wounds, etc. Incident conditions potentially indicative of a systemic autoimmune disorder occurred in 245 (2.3%) of 10,706 female vaccinees and 218 (2.3%) of 9,412 placebos. The respective rates for males were 43 (1.4%) of 3,092 and 32 (1.4%) of 2,303.

The ACIP has recommended permissive use of HPV4 in males 9 to 26 years of age, meaning that it may be given (as opposed to should be given) to reduce the likelihood of acquiring genital warts.2

References

There is now a second option for vaccination against cervical cancer. Cervarix8 was approved by the FDA in October 2009 for prevention of cervical cancer, cervical intraepithelial neoplasia (CIN), and cervical adenocarcinoma in situ caused by HPV types 16 and 18 in females 10 to 25 years of age.1 The vaccine contains recombinant-derived L1 proteins from HPV, which self-assemble into virus-like particles. Unlike HPV4, this 2-valent vaccine (HPV types 16 and 18 [HPV2]) does not contain proteins from HPV types 6 and 11 and therefore does not prevent genital warts (see The Vaccine Quarterly 2007;11[3]:3–4,19 for further discussion of cervical cancer vaccines). There are two other important differences between HPV2 and HPV4: (1) the L1 proteins of HPV2 are purified from insect cells infected with a Baculovirus vector carrying the L1 genes, as opposed to yeast cells that express the genes for HPV4; and (2) HPV2 is formulated with an adjuvant called AS04, as opposed to alum for HPV4. AS04 is composed of 3-O-desacetyl-4′-monophosphoryl lipid A (MPL, a derivative of bacterial lipopolysaccharide) adsorbed to an aluminum hydroxide salt. MPL activates Toll-like receptor-4 on antigen-presenting cells (APCs), promoting cytokine expression, antigen presentation, and migration of APCs to lymph nodes (see The Vaccine Quarterly 2008;2[4]:3–4,8 for further discussion of adjuvants). HPV2 is the first vaccine approved in the U.S. with an adjuvant other than alum, although an AS04-adjuvanted HepB has been licensed elsewhere.

The ACIP-recommended schedule for HPV2 is 3 doses (0.5 mL each) given intramuscularly at 0, 1–2, and 6 months (note that the package insert says 0, 1, and 6 months).2 Each dose contains 20 mcg of HPV type 16 L1 protein, 20 mcg of HPV type 18 L1 protein, 50 mcg of MPL, and 0.5 mg of aluminum hydroxide. Excipients and contaminants include sodium chloride, sodium dihydrogen phosphate dihydrate, and residual amounts of insect cell, bacterial cell, and viral proteins. The vaccine is supplied in pre-filled syringes and single-dose vials without preservative (the tip and cap of the syringes contain latex but the vial stopper does not).

Efficacy of HPV2 in preventing high-grade cervical lesions (CIN2/3) or AIS was assessed in 2 studies that enrolled nearly 20,000 females 15 to 25 years of age. The first study enrolled 1,113 women who were naïve for HPV infection as assessed by DNA assays for oncogenic HPV types on cervical specimens, serology for antibodies to HPV 16 and 18, and cytology. Follow-up at a mean of 5.9 years was available for 776 subjects. Efficacy against HPV 16- or 18-related CIN2/3 or AIS was 100% (98.67% CI 28.4, 100). Efficacy against 12-month persistent infection with HPV 16 or 18 was 100% (98.67% CI 74.4, 100).

The second study enrolled women regardless of baseline HPV DNA status, serostatus, or cytology, thus including women who were HPV-naïve and non-naïve (i.e., those with current infection or prior exposure). A total of 18,665 women were randomized to receive HPV2 or HepA at 0, 1, and 6 months. Prior to vaccination, 73.6% of subjects were naïve to HPV-16 and/or 18, and the mean follow-up period after the first dose was 39 months.

Among women who were HPV-naïve at baseline and were vaccinated according to protocol, efficacy against HPV 16- or 18-related CIN2/3 or AIS was approximately 93% (Table 2). Among all women who received at least 1 dose of vaccine, regardless of current infection with or prior exposure to HPV 16 or 18 and including all cases starting on Day 1, efficacy against HPV 16- or 18-related CIN2/3 or AIS was 52.8% (96.1% CI 37.5, 64.7); the vast majority of cases that occurred were due to prevalent infection at the time of vaccination rather than incident infection after vaccination. Among all women who received at least 1 dose of vaccine, regardless of current infection with or prior exposure to any HPV type and including all cases starting on Day 1, efficacy against CIN2/3 or AIS related to any HPV type was 30.4% (96.1% CI 16.4, 42.1). This approximates what might be seen in the general population, where women who are vaccinated might already be infected with oncogenic HPV types and where exposures to many oncogenic types may occur.

Among women who were vaccinated according to protocol, efficacy against CIN2/3 or AIS caused by 12 non-vaccine types (considered as a group) was 54.0% (96.1% CI 34.0, 68.4). When lesions that contained HPV 16 and/or 18 DNA were excluded in the outcomes analysis, efficacy against CIN2/3 or AIS caused by 12 non-vaccine types (considered as a group) was 37.4% (96.1% CI 7.4, 58.2); arguably, if the vaccine did not protect against any of these other types, this number should have been 0%. Among women who were vaccinated according to protocol and were HPV-31 DNA negative through month 6, efficacy against CIN2/3 or AIS caused by HPV 31 was 89.4% (99.7% CI 29.0, 99.7) when lesions also containing 16 and 18 were excluded. Importantly, though, HPV2 is labeled only for prevention of lesions due to vaccine serotypes.

Virtually all subjects developed antibodies to HPV 16 and 18 as measured by enzyme-linked immunosorbent assay as well as a pseudovirion-based neutralization assay. Persistent responses were seen in 98% when measured 76 months post-vaccination. The immune response in girls 10 to 14 years of age was non-inferior to older women, allowing the assumption that similar disease protection will ensue.

Local reactions (pain, 91.8%; redness, 48.0%; swelling, 44.1%) occur more frequently among HPV2 recipients than placebos; the majority of reactions are mild or moderate in intensity. Approximately half of vaccinees experience fatigue, headache, and myalgia. In a pooled safety analysis, serious adverse events were reported in 5.3% of 16,142 vaccinees and 5.9% of 13,811 placebo...
during a follow-up period of 7.4 years. In a database of studies including 57,323 females, there were 20 deaths among HPV2 recipients and 17 among control recipients. The causes of death were as expected for the patient population under study (e.g., motor vehicle accidents, suicides, homicides, neoplasms, etc.). In the largest randomized controlled trial in women 15 to 25 years of age, new-onset autoimmune disease was seen in 78 (0.8%) of 9,319 vaccinees as compared to 77 (0.8%) of 9,325 HepA controls. These data provide further reassurance that HPV vaccines are safe (see review of the article by Slade, et al. elsewhere in this issue).

The ACIP recommends HPV vaccination for all females at 11 or 12 years of age.2 The series can be started as early as 9 years of age and should also be given to unvaccinated females 13 through 26 years of age (these recommendations slightly extend the labeled age for HPV2 from 10 to 25 to 9 to 26). HPV4 should be used if protection against genital warts is also desired. While HPV4 has also been shown to protect against vulvar and vaginal cancers and precancers, there is no preference for one vaccine over the other for prevention of cervical cancer. The minimum interval between Dose 1 and Dose 2 is 4 weeks for both vaccines. Dose 3 should be given ≥12 weeks after Dose 2 and ≥24 weeks after Dose 1. Whenever possible, the same product should be used for the whole series, and the schedule does not need to be reinitiated if interrupted.

HPV vaccines can be given at any time with respect to any other vaccines. They should not be given during pregnancy, but women do not need to be tested before vaccination. Finally, remember that syncope can occur after vaccination, so 15 minutes of observation is a good idea. Particularly predisposed individuals can be vaccinated while seated or lying down.

### Table 2. Efficacy of HPV2 in Preventing Cervical Lesions Associated With HPV 16 and 18 in Women Vaccinated According to Protocol†

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HPV2 Number of Cases</th>
<th>HPV2 CI*</th>
<th>HepA Control Number of Cases</th>
<th>HepA Control Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN2/3 or AIS</td>
<td>7,344</td>
<td>4</td>
<td>7,312</td>
<td>56</td>
</tr>
<tr>
<td>CIN1/2/3 or AIS</td>
<td>7,344</td>
<td>8</td>
<td>7,312</td>
<td>96</td>
</tr>
</tbody>
</table>

†Patients who had normal cytology or low-grade lesions at baseline, were not infected with HPV-16 or 18 through the period of vaccination, and received 3 doses.

* The confidence intervals noted for the final analyses (not the usual 95% CI) result from statistical adjustment for analyses previously conducted.

Table adapted from Cervarix® package insert.

References
CME QUIZ

To earn CME credit, you must read the article and the reviews and complete the quiz, answering at least 70% of the questions correctly, and evaluation below. Mail a photocopy of the completed page to Lippincott Continuing Medical Education Institute, Inc., Two Commerce Square, 2001 Market Street, 3rd Floor, Philadelphia, PA 19103–7042. Only the first entry will be considered for credit and must be received by LCME by March 31, 2011. Acknowledgment will be sent to you within 6 weeks of participation.

1. Most invasive meningococcal disease in infants is caused by serogroup B strains.
   - True
   - False

2. A personal history of Guillain-Barré syndrome is a contraindication to receiving MCV4-D.
   - True
   - False

3. The cocooning strategy for prevention of pertussis in infants is important because of which of the following?
   - a. Many women of childbearing age did not receive adequate childhood vaccination against pertussis.
   - b. Household contacts, including mothers, are the most common source of pertussis infection of infants.
   - c. Vaccination of all adults against pertussis is not recommended due to high cost.

4. Cost comparisons of 2 vaccine products against the same infection(s) are most likely to be affected by which of the following?
   - a. Natural history of the infection and its complications
   - b. Study follow-up duration of less than 5 years after vaccination
   - c. Differences in estimates of efficacy of fewer doses than the full series
   - d. Small differences in cost between the full series of the 2 products

5. In the study of electronic health alerts reminding clinicians to offer influenza vaccine to children with asthma, which of the following characteristics were associated with increased likelihood of vaccination?
   - a. Visit in January through March
   - b. Fever
   - c. Previous receipt of influenza vaccine
   - d. Caucasian

6. VAERS defines a serious event as one that is life-threatening, or results in death, permanent disability, a congenital anomaly, hospitalization, or prolongation of hospitalization.
   - True
   - False

7. Which of the following rabies prophylaxis recommendations is most appropriate for patients who are possibly exposed to animals?
   - a. Pre-exposure human prophylaxis with rabies vaccine and rabies immune globulin alone
   - b. Post-exposure human prophylaxis with rabies vaccine and rabies immune globulin (RPEP) alone
   - c. Post-exposure wound care alone
   - d. RPEP and wound care

8. Febrile convulsions occurred more commonly among MMRV than MMR plus VAR recipients during which time frame?
   - a. 0 to 4 days postvaccination
   - b. 5 to 12 days postvaccination
   - c. 0 to 30 days postvaccination
   - d. 0 to 60 days postvaccination

9. After introduction of the DTaP-IPV/Hib vaccine in Canada, which of the following statements is true of disease incidence during the late 1990s and early 2000s?
   - a. Pertussis increased and invasive Haemophilus type b disease remained low.
   - b. Pertussis decreased and invasive Haemophilus type b disease remained low.
   - c. Pertussis decreased and invasive Haemophilus type b disease increased.
   - d. Pertussis and invasive Haemophilus type b disease both increased.

10. The most common reason cited by U.S. studies for health care workers not being immunized against influenza was lack of availability of the vaccine.
    - True
    - False

Your completion of these activities includes evaluating them. Please complete the questions below.

1. Please rate these activities (1 – minimally, 5 – completely)
   These activities were effective in meeting the educational objectives.
   - 1
   - 2
   - 3
   - 4
   - 5

   These activities were appropriately evidence-based.
   - 1
   - 2
   - 3
   - 4
   - 5

   These activities were relevant to my practice.
   - 1
   - 2
   - 3
   - 4
   - 5

2. How many of your patients are likely to be impacted by what you learned from these activities?
   - <20%
   - 20%–40%
   - 40%–60%
   - 60%–80%
   - >80%

3. Do you expect that these activities will help you improve your skill or judgment within the next 6 months? (1 – definitely will not change, 5 – definitely will change)
   - 1
   - 2
   - 3
   - 4
   - 5

4. How will you apply what you learned from these activities (mark all that apply):
   - In diagnosing patients
   - In monitoring patients
   - In making treatment decisions
   - In educating students and colleagues
   - As a foundation to learn more
   - In educating patients and their caregivers

5. How committed are you to applying these activities to your practice in the ways you indicated above? (1 – minimally, 5 – completely)
   - 1
   - 2
   - 3
   - 4
   - 5

6. Did you perceive any bias for or against any commercial products or devices?
   - Yes
   - No

7. How long did it take you to complete these activities?
   - Hour(s)________ Minutes________

8. What are your biggest clinical challenges related to vaccination?

   ________________________________________________________________
   ________________________________________________________________
   ________________________________________________________________
   ________________________________________________________________

   YES! I am interested in receiving future CME activities from Lippincott CME Institute! (Please place a check mark in the box.)

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