

Emerging vaccines

Evidence and considerations for practice integration

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New vaccines are available to your patients. This paper will assist you in formulating your own best practices regarding immunization and will provide you with the necessary information to make well-informed evidence-based decisions.

Physicians should focus on concerns about immunization raised by patients or caregivers. Although health professionals have many of their own concerns (efficacy, length of immunity, cost, side effects, etc) that determine their final decisions, patients and caregivers often have different priorities. For example, the most important factors affecting parents' decisions to vaccinate their children are health care providers' recommendations and the side effects of the vaccines. This paper will thus focus mainly on answering caregiver questions: Is it recommended? What are the side effects? Other important concerns of efficacy and length of immunity will also be addressed. All the vaccines have level I evidence supporting immunogenicity and safety. Where efficacy is reported, level I evidence supports the data.

As Canadian recommendations from the National Advisory Committee on Immunization (NACI) become available, physicians should check the NACI website for new information (www.phac-aspc.gc.ca/naci-ccni/). In some instances, American recommendations are available and will be referenced below. The age groups included in the landmark studies provide the likely target populations for the vaccines.

Quadrivalent conjugate meningococcal vaccine

Meningococcal infection is most commonly caused by serogroups A, B, C, Y, and W-135. In North America, most illness is caused by serogroups B and C.¹ No vaccine for serogroup B is available for patients at this time. A vaccine for serogroup C is currently recommended for Canadian patients.¹ A conjugate intramuscular quadrivalent vaccine that protects against serogroups A, C, Y, and W-135 (Menactra) was approved for use in Canada in May 2006 for those between ages 2 and 55. It is provided in 0.5 mL vials and is offered as a single dose. Menomune is the polysaccharide version.

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Is the vaccine recommended? The incidence of serogroup Y meningococcal disease in Canada between 1995 and 2004 was 0.09 cases per 100 000 population per year (approximately 1 per million population per year). The median age of affected patients was 45 years. The incidence of meningococcal disease caused by serogroup W-135 was 0.03 per 100 000 population per year, and the incidence caused by serogroup A was 0.002 per 100 000 population per year. In the May 2007 *Canada Communicable Disease Report*, NACI published the following statement regarding Menactra:

Because of the relative rarity of serogroups A, Y and W135 in the population and the possible risk of [Guillain-Barré syndrome] related to Menactra, the use of this vaccine should be considered only in individuals or circumstances when serogroups A, Y or W135 occur with increased frequency.... For most jurisdictions, the current epidemiology of serogroups A, Y and W135 does not support the routine use of Menactra.²

The statement did, however, recommend that the vaccine be offered to high-risk individuals between 2 and 55 years of age, including the following:

- those with selected immune deficiencies;
- travelers, those with a high risk of exposure, military recruits; and
- those with HIV infection.

Among high-risk children between 2 and 10 years of age for whom the vaccine is recommended, a dose of Menactra should be given followed by a dose of meningococcal C vaccine (at least 1 month later). Among adults older than 56 years of age, Menactra can be considered if indicated (level III evidence).

Levels of evidence

Level I: At least one properly conducted randomized controlled trial, systematic review, or meta-analysis

Level II: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study

Level III: Expert opinion or consensus statements

It is of interest to note that, while the United States does not have monovalent meningococcal C vaccine, regulators there have approved the quadrivalent meningococcal vaccine. The American Advisory Committee on Immunization Practices and the American Academy of Pediatrics recommend that all 11- to 18-year-olds receive the quadrivalent vaccine.¹

What are the side effects of the vaccine? The safety of the quadrivalent meningococcal vaccine has been demonstrated with 9 controlled clinical trials involving more than 10 000 patients.³ The rates of systemic adverse events were similar to those of the polysaccharide quadrivalent meningococcal vaccine. Redness and induration were the typical reactions. Systemic reactions included headache and fatigue (40%). No serious systemic reactions were reported in any of the trials. More than 7 million American patients have received Menactra, and surveillance has identified a possible clustering of Guillain-Barré syndrome (GBS) among those receiving the vaccine.⁴ In its statement,² NACI referred to data provided by the US Centers for Disease Control and Prevention (CDC): "The CDC estimated that 1.25 (95% confidence interval 0.058-5.99) excess cases of GBS can be estimated for every 1 million doses of vaccine."

The CDC declared that there was substantial uncertainty regarding the data, owing to the very small risks of both meningococcal disease and GBS.⁴ The CDC did not make any changes to its recommendation that every teenager receive Menactra. In February 2007, the CDC risk estimate was only 0.89 extra cases per million doses.

The safety of the quadrivalent conjugate vaccine has been demonstrated among children who received the monovalent C vaccine 12 months earlier.⁵ Concomitant usage of diphtheria and tetanus vaccine is safe and immunogenic.⁶ Studies with tetanus, diphtheria, and acellular pertussis vaccine will soon be available.

As the incidence and serogroup distribution of meningococcal disease varies from region to region and from year to year, the Canadian recommendations might need to be re-assessed. As more information becomes available about the possible relationship between GBS and Menactra, safety concerns will need to be reevaluated. Large-scale population studies of efficacy might reveal a substantially higher risk of morbidity and mortality among unvaccinated patients than among vaccinated patients. When the safety and efficacy are established, caregivers and patients should be able to decide for themselves if the incidence is high or low relative to their own degree of relative risk acceptance.

At this time, health providers might consider individually recommending Menactra to teenagers who want the broadest coverage possible (and to children for boosting and broadening their coverage).

Will the vaccine protect my child? The data demonstrate priming, antibody persistence, memory, and boosting.³ There are no placebo-controlled efficacy trials to date. Studies have generally compared the new conjugate vaccine to the older polysaccharide vaccine. Post-marketing studies of large populations in the United States might soon be available. We should remind parents of the incredible efficacy of other conjugate vaccines including the *Haemophilus influenzae* type b and pneumococcal vaccines.

How long will the vaccine protection last? The length of protection often determines the best age at which to give vaccines. At this time, the published length of protection is more than 3 years; however, the Advisory Committee on Immunization Practices suggests that protection might last up to 8 years.¹ Inform patients that it might be necessary to include a booster dose in the future and that ongoing surveillance will determine if it will be necessary. By the time it would be required, the booster could even be a newer, different vaccine.

Rotavirus vaccine

Rotavirus is the most important cause of diarrhea in children. It kills half a million children annually in developing countries.⁷ Rotavirus is the most common infectious cause of hospitalization for diarrhea in North America. Protection is now available to infants in the form of either an oral monovalent human vaccine or a pentavalent human-bovine vaccine. From a caregiver prospective, rotavirus is a common cause of illness leading to emergency room visits and hospitalization.⁸ The risk to an individual child of hospitalization from rotavirus is estimated to be 1 in 106.⁸

Is the vaccine recommended? In August 2006, a live, oral pentavalent rotavirus vaccine (RotaTeq) was approved in Canada. The first dose is to be given no later than 3 months of age and the last dose by 8 months (to avoid the period of intussusception risk). There are no preservatives or thimerosal in the vaccine. The American Academy of Pediatrics has endorsed the recommendations of the Advisory Committee on Immunization Practices that an oral (2 mL) pentavalent rotavirus vaccine be given universally to infants at 2, 4, and 6 months of age.⁹

A rotavirus vaccine had been recommended in the past by the American Academy of Pediatrics.¹⁰ The recommendation was withdrawn after that particular rhesus-based vaccine was associated with intussusception.¹¹ Two new emerging vaccines have recently

completed safety and efficacy trials. A monovalent human vaccine has been studied as 2 oral doses, given at 2 and 4 months of age.¹² A pentavalent human-bovine vaccine has been studied as 3 oral doses, given at 2, 4, and 6 months of age.¹³ The pentavalent vaccine is currently available in North America. Concomitant delivery with other vaccines is acceptable.

What are the side effects of the vaccine? With an earlier vaccine being withdrawn from the market, safety will be an important aspect of your counseling to caregivers when making this particular recommendation. Both of these new vaccines have been studied in large clinical trials to establish their safety.^{12,13} The monovalent human vaccine was evaluated among more than 63 000 healthy infants in Latin America and Finland. The pentavalent human-bovine vaccine was studied among more than 68 000 infants from 11 countries, including the United States. There was no increased risk of intussusception in the vaccinated population in either study. No other serious side effects were reported more commonly among the vaccinated groups than among the placebo groups. Minor side effects included fever, vomiting, and diarrhea.

In February 2007, the US Food and Drug Administration released a Public Health Notification encouraging the reporting of intussusception related to RotaTeq. After 3.5 million doses were distributed, the number of cases of reported intussusception did not exceed the rate for the unvaccinated population. The CDC Vaccine Safety Data Link and Merck, the company behind the product, are conducting 2 further studies of 90 000 and 40 000 infants, respectively.

Will the vaccine protect my child? Both emerging vaccines proved efficacious. Efficacy against severe rotavirus-associated diarrhea was cited as 98% against the vaccine serogroup for the pentavalent vaccine. Hospitalization for diarrhea of any cause was reduced by 63% by the pentavalent vaccine. Pentavalent rotavirus vaccine reduced the serogroup-specific incidence of office visits by 86%, emergency department visits by 94%, and hospitalizations for rotavirus gastroenteritis by 96%.¹³

How long will the vaccine protection last? Although the length of protection from illness is a common concern of caregivers, the issue is less important with this vaccine. Rotavirus-associated diarrhea is most common in the first and second year of life.¹² The human-bovine pentavalent vaccine has demonstrated continued efficacy over 2 seasons, providing protection when it is needed most.

Human papillomavirus vaccine

Human papillomavirus (HPV) causes more than 470 000 cases of cervical cancer yearly. In the United

States and Europe more than 35 000 women die each year from the disease.¹⁴ In Canada, about 1400 new cases of cervical cancer are diagnosed each year, with about 400 deaths occurring annually.¹⁵ A bivalent vaccine will prevent against HPV-related cervical cancer, and a quadrivalent vaccine will prevent against HPV-related cervical cancer and HPV-related genital warts. The quadrivalent (types 6, 11, 16, 18) vaccine (Gardasil) was approved for use in Canada in July 2006. It is provided in a 0.5 mL vial or syringe and is given intramuscularly in 3 doses at 0, 2, and 6 months. Gardasil can be given with hepatitis B vaccine; studies with formulations of pertussis vaccine are pending.

Is the vaccine recommended? In February 2007, the NACI provided the Public Health Agency of Canada with the following recommendations for HPV vaccination¹⁶:

- all females 9 to 13 years of age should receive the vaccine;
- the vaccine would benefit females 14 to 26 years of age;
- the vaccine should be considered in individual circumstances for females older than 26 years of age; and,
- the vaccine is recommended for females who are already sexually active, who have had prior abnormal Papanicolaou test results or HPV, or who have had cervical cancer or genital warts.

Gardasil has recently been made available to patients at specific ages through provincial funding programs. If your patient is past the age of public funding, consider facilitating vaccination through private payment. The American Academy of Pediatrics and the Society for Adolescent Medicine have endorsed the recommendations of the Advisory Committee for Immunization Practices for HPV vaccine to be administered to young women at 11 to 12 years of age.¹⁷

Currently, there is no Canadian recommendation for boys and men to be vaccinated. In North America the HPV vaccine is currently recommended only for girls and women; Europe and Australia have recommended vaccination for both females and males.

It is relevant to note that, when introduced, the rubella vaccine was given only to females to prevent congenital rubella syndrome. This strategy did not substantially reduce rubella disease. A new strategy of immunizing females and males later proved extremely effective. We might well need to vaccinate males with HPV vaccine to achieve a similarly dramatic reduction in HPV infection on a population level.

When questioned in focus groups, parents were generally positive about the vaccine but believed their children not to be at risk.¹⁸ When counseling patients and caregivers about the likelihood of their children becoming infected with HPV, inform them that approximately

70% of sexually active women will become infected during their lifetimes. Estimates indicate that approximately 60% of sexually active women become infected with HPV in only a 5-year follow-up period.¹⁹ Sexual intercourse is not necessary for transmission. Approximately 33% of male American university students are infected with HPV.¹⁹ The most commonly acquired type is HPV-16; HPV-16 and HPV-18 are the most common causes of cervical cancer. Both vaccines coming to market will cover these types. Vaccination will help prevent the second most common type of cancer in women.

Further, 90% of anogenital warts are caused by HPV-6 or HPV-11. Genital warts from HPV occur in 1% to 2% of young adults. Treatment is painful and recurrences are common.²⁰ Only the quadrivalent vaccine will cover HPV-6 and HPV-11 (in addition to HPV-16 and HPV-18).

What are the side effects of the vaccine? We need to keep in mind the importance of explaining side effects to caregivers and, in the case of this vaccine, to patients as well. The quadrivalent vaccine was studied in young women in randomized double-blind placebo-controlled trials.²¹ Among 11 000 women receiving the vaccine, only local injection-site pain, erythema, and systemic headache reactions were observed. Most events were of mild or moderate intensity. No serious vaccine-related adverse events occurred. As this vaccine has been recommended in the United States, a large number of patients will be vaccinated and the side effects profile will be further evaluated as time goes by.

Will the vaccine protect my child? Phase 2 and 3 studies are available for evaluation. All women immunized developed antibodies. There were 90% fewer HPV infections overall. The vaccine was 100% effective against clinical disease.²¹ In a study of 2392 young women given an HPV-16 vaccine, no cases of HPV infection occurred in the vaccinated group over a median of 17 months (3.8 per 100 women-years in the placebo group).²² Large-scale studies are under way.

How long will the vaccine protection last? As of 2006, the length of immunity (bivalent and quadrivalent vaccines) has been established only at a minimum of 5 years. As the vaccine is made available to the market, further length-of-immunity data will become available.²¹

Herpes zoster vaccine

Approximately 1 million cases of herpes zoster occur in the United States each year. (It is not a reportable disease).²³ The incidence and severity of shingles increase with advancing age; complications such as postherpetic neuralgia occur in more than 50% of older patients with herpes zoster.²⁴ The pain associated with shingles and postherpetic neuralgia can be disabling and prolonged.

Antiviral therapy does not prevent the morbidity of postherpetic neuralgia.²⁵

Is the vaccine recommended? A vaccine to prevent herpes zoster and postherpetic neuralgia will soon be available to your patients. It will likely be indicated for adults older than 60 years of age. It will be a vaccine similar to that used to vaccinate children against varicella but much more potent.

What are the side effects of the vaccine? A recent randomized double-blind placebo-controlled trial of more than 38 000 adults over 60 years of age was conducted using a live attenuated vaccine. More than 95% of the subjects completed the study. Reactions at the injection site were slightly more frequent among the vaccinated group than among the placebo group but were mild in nature. There was no increase in the incidence of serious adverse events over placebo recipients.²⁶

Will the vaccine provide protection? In the study mentioned above, the incidence of herpes zoster was reduced by 51%. The incidence of postherpetic neuralgia was reduced by 67%. The vaccine likely achieved this reduction in disease by boosting immunity to varicella zoster virus in vaccinated patients.²³

How long will the vaccine protection last? Currently, the length of immunity is known to be more than 3 years. Further follow-up will be necessary to determine the true length of immunity that can be confidently reported to patients.

Varicella vaccine

In the near future, the incidence of varicella disease should decline rapidly. The Advisory Committee on Immunization Practices in the United States has recommended that every child receive 2 doses of varicella vaccine.²⁷ The second dose should be given approximately 3 months after the first dose. To facilitate giving 2 doses of varicella vaccine, a combined measles, mumps, rubella, and varicella vaccine is now available in the United States. It is recommended at 12 months of age. There are no Canadian recommendations at this time for the combined vaccine.

Conclusion

By focusing on patient and caregiver concerns about immunization, health providers will serve their patients more effectively. Patients and caregivers need to know the potential side effects of a vaccine at the time that it is being recommended.

As the emerging vaccines described above become available in developed countries, the information included will allow practitioners to make well-informed evidence-based decisions regarding best practices. Our

focus should then turn toward providing these vaccines more widely in developing countries. 

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Competing interests

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