Objective To provide family physicians with information on the efficacy, safety, public health effects, and cost-effectiveness of the 9-valent human papillomavirus (HPV) vaccine.

Quality of evidence Relevant publications in PubMed up to May 2015 were reviewed and analyzed. Most evidence cited is level I (randomized controlled trials and meta-analyses) or level II (cross-sectional, case-control, and epidemiologic studies). Government reports and recommendations are also referenced.

Main message The 9-valent HPV vaccine, which protects against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, is safe and effective and will further reduce the incidence of HPV infection, as well as HPV-related cancers. It can also indirectly protect unvaccinated individuals through herd immunity. With an effective vaccination program, most cervical cancers can be prevented. Analyses show that the cost-effectiveness of the 9-valent HPV vaccine in female patients is comparable to the original quadrivalent HPV vaccine (which protects against HPV types 6, 11, 16, and 18) currently in use. However, the usefulness of vaccinating male patients with the 9-valent HPV vaccine needs further investigation.

Conclusion The 9-valent HPV vaccine offers more protection against HPV than the quadrivalent HPV vaccine does and is as safe. Analysis of cost-effectiveness favours its use, at least in adolescent girls. Therefore, physicians should recommend the 9-valent HPV vaccine to patients instead of the quadrivalent HPV vaccine.
programs have the potential to alleviate the burden of HPV-associated diseases.

Until the recent approval of the 9-valent HPV vaccine (directed to protect against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58), the vaccines for HPV prevention authorized for use in Canada were the bivalent vaccine (directed against HPV types 16 and 18) and the quadrivalent HPV vaccine (directed against HPV types 6, 11, 16, and 18).

All provinces and territories have introduced the quadrivalent HPV vaccine to their routine immunization schedules for adolescent girls. Some provinces have also introduced vaccination programs for boys.

In clinical trials, the quadrivalent HPV vaccine was found to be safe and efficacious (level I). The effects of HPV vaccination programs on population health have already been observed in the form of reduced incidences of HPV infections, genital warts, and HPV-attributed precancerous lesions (level II).

For instance, a Danish cohort study assessing the effectiveness of Denmark's nationwide HPV vaccination program found that the risk of developing cervical dysplasia (cervical intraepithelial neoplasia grades 2/3 and 3) was reduced by up to 80% in a vaccinated cohort when compared with a nonvaccinated cohort (level II). However, it is too early to study the effects of vaccination on cervical cancer rates, as it takes decades for HPV infection to progress to invasive cervical cancer. With HPV vaccination showing positive outcomes, the new 9-valent HPV vaccine was developed to increase protection against 5 more strains (ie, HPV types 31, 33, 45, 52, and 58), for a total of 9 HPV strains. Such a vaccine has the potential to offer protection against approximately 90% of cervical cancers, up from the 70% offered by the quadrivalent HPV vaccine (level II).

The 9-valent HPV vaccine is similar in composition to the quadrivalent vaccine, using viruslike particles to elicit immune responses.

Quality of evidence

A PubMed search was conducted for relevant articles up to May 2015 using the following key words: HPV vaccine, HPV9, Gardasil, Gardasil 9, nonavalent HPV, and 9-valent HPV. Attention was especially paid to articles pertaining to randomized clinical trials, systematic reviews, epidemiologic studies, and safety reviews. Most of the evidence cited is level I (randomized controlled trials and meta-analyses) or level II (cross-sectional, case-control, and epidemiologic studies). Government reports from the health agencies of Canada and the United States were also reviewed.

Main message

Efficacy. Owing to its increased protection against HPV strains, the 9-valent vaccine has the potential to further reduce the incidence of HPV infection. A cross-sectional study on the relative contribution to cervical cancer and precancerous lesions of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 found that these 9 types were responsible for 95.5% of all cervical lesions in North America. Human papillomavirus types 31, 33, 45, 52, and 58 caused 16.9% of total lesions (level II). A US assessment of the types of HPV in cancers found that these 5 types were responsible for between 4.2% and 18.3% of neoplasias of the cervix, vagina, vulva, anus, penis, oral cavity, and oropharynx. The assessment indicates that the use of the 9-valent vaccine will increase the percentage of preventable HPV-associated cancers from 63.4% to 73.5%, assuming 100% coverage and efficacy (level II).

These studies indicate that an effective vaccine against the 9 aforementioned HPV types will provide additional protection against various HPV-associated cancers above and beyond the current protection provided by the quadrivalent vaccine.

The 9-valent HPV vaccine was recently approved by Health Canada for females aged 9 to 45 and males aged 9 to 26. In a clinical trial based on a phase 2/3 study design, the 9-valent vaccine was found to provide efficacious protection against HPV types 31, 33, 45, 52, and 58, and generated noninferior antibody response against HPV types 6, 11, 16, and 18 in comparison with the quadrivalent vaccine (level I). This randomized, double-blinded study involved more than 14 000 women aged 16 to 26 worldwide receiving 3 doses of either the 9-valent or the quadrivalent HPV vaccine. Swabs of urogenital tissues were collected at regular intervals for up to 54 months and tested for HPV infection. The rate of high-grade neoplasias and cancers of the cervix, vulva, and vagina associated with the 5 additional HPV types was 0.1 per 1000 person-years in the per-protocol population (using the 9-valent vaccine) compared with 1.6 per 1000 person-years in the quadrivalent group (level I). This result translates to an efficacy of 96.7% (95% CI 80.9% to 99.8%). The incidence of persistent HPV infection related to the 5 additional HPV types was 2.1 per 1000 person-years in the per-protocol population and 52.4 per 1000 person-years in the quadrivalent group. The overall rates of cervical, vulvar, or vaginal neoplasias or cancers, irrespective of HPV types, were 2.4 per 1000 person-years in the 9-valent vaccine group and 4.2 per 1000 person-years in the quadrivalent vaccine group (level I). The geometric mean titre (GMT) against the 4 shared HPV types for the 9-valent vaccine group was not inferior to that of the quadrivalent vaccine group (level I).

In addition, immunobridging trials were conducted to gauge the efficacy of the vaccine in adolescents (since the trial population was older than the target population). The 9-valent HPV vaccine was found to generate noninferior GMT in both girls and boys aged 9 to 15 (level I). Another study found that the 9-valent vaccine was also effective in young males aged 16 to 26 (level I). The GMT for the 9-valent vaccine was not
affected by the concomitant administration of meningococcal (groups A, C, Y, and W-135) polysaccharide diphtheria toxoid conjugate vaccine and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (level I). These results indicate that the 9-valent vaccine is efficacious in the targeted male and female adolescent population and is not disrupted by concomitant inoculation with other vaccines.

Safety. Adverse effects of the 9-valent vaccine include injection site–related pain, swelling, and erythema. Recipients of the 9-valent vaccine were slightly more likely to experience these adverse events than recipients of the quadrivalent vaccine (90.7% vs 84.9%) were, possibly owing to the higher amounts of viruslike particles and adjuvants in the 9-valent vaccine. Rates of systemic events such as headaches, pyrexia, nausea, and fatigue were similar between the 2 groups (55.8% for 9-valent HPV vaccine vs 54.9% for quadrivalent HPV vaccine). Pregnancy outcomes and congenital anomalies were also similar (level I). Out of more than 14,000 vaccine recipients, only 2 recipients from each group experienced a serious vaccine-related adverse event. Five deaths were recorded from each group but none was judged to be vaccine related (level I). Subsequent immunobridging trials also found similarly low levels of vaccine-related severe adverse events and no vaccine-related deaths (level I). Based on these data, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention deemed the 9-valent HPV vaccine to be safe and well tolerated.

Cost-effectiveness. Two studies examined the potential cost-effectiveness of the 9-valent HPV vaccine using the model of HPV infection that had previously been used to compare the bivalent and quadrivalent HPV vaccines (level II). The model was calibrated to fit Canadian epidemiologic data and calculated the cost per quality-adjusted life-year (QALY) gained. The model first used a baseline scenario of vaccinating 10-year-old girls, with 80% protection and 95% efficacy, at a cost of $95 per dose, with limited quadrivalent vaccine cross-protection against 9-valent vaccine strains, and a 20-year duration. In this scenario, the 9-valent vaccine is more cost-effective (cost per QALY gained of $12,208 for the 9-valent vaccine vs cost per QALY gained of $15,528 for the quadrivalent vaccine) (level II). This cost-effectiveness advantage was maintained even in situations where the duration of protection and efficacy for the 9-valent vaccine was lower. However, the advantage is nullified if the cost per dose of the 9-valent HPV vaccine exceeds that of the quadrivalent HPV vaccine by $11 or more (level II). Therefore, the 9-valent vaccine could be a more cost-effective alternative to the quadrivalent vaccine if the pricing is comparable. In Ontario, the cost of the 9-valent vaccine for patient purchase—approximately $567 in local pharmacies in Hamilton—is not appreciably different from that of the quadrivalent vaccine; however, the cost for the provincial government might be different. There has been discussion of reducing the vaccine from a 3-dose to a 2-dose schedule, although evidence is inconclusive (level I). Future studies might provide enough data to change the dosing schedule, thus altering the cost-effectiveness data. With an increase in HPV vaccinations, the resultant decrease in the prevalence of HPV infection and its associated cancers might allow screening (ie, Papanicolaou tests) to be less frequent, leading to a further reduction in health care costs.

While the National Advisory Committee on Immunization currently recommends the quadrivalent HPV vaccine for males 9 to 26 years old, publicly funded programs for male vaccination only exist in Alberta and Prince Edward Island. Although HPV is currently responsible for 50% of penile cancer, 90% of anal cancer, and 35% of oropharyngeal cancer in Canada, the average annual incidences of these cancers are low in comparison to cervical cancer (1.6 per 100,000 for anal cancer vs 10.1 per 100,000 for cervical cancer) (level II). However, there is still a need for a Canada-specific analysis to determine the cost-effectiveness of vaccinating males against HPV. Studies from elsewhere have highly variable results, with some supporting and others refuting the cost-effectiveness of vaccinating males (level II). These differences in results are likely due to differences in study populations, disease-incidence projections, variations in the cost of vaccination and treatment, and the type of model used to make the predictions. The cost-effectiveness of HPV vaccination for males in Canada should be examined to help guide policy. However, because the additional 5 types of HPV included in the 9-valent vaccine account for a much smaller proportion of HPV-related cancers in men than women (level II), it might not be necessary for the 9-valent HPV vaccine to be used in males. The Advisory Committee on Immunization Practices reports implied that the current quadrivalent HPV vaccine would likely provide sufficient protection for males (level II).

Public health. The 9-valent vaccine increases protection against HPV with minimal additional cost and harm. The Society of Obstetricians and Gynaecologists of Canada recommends HPV vaccinations using the 9-valent HPV vaccine for all Canadians in indicated age groups. Because the 9-valent vaccine was only recently approved, research evidence is lacking on whether or not vaccination programs with the 9-valent vaccine can lead to more reduction of HPV-related cancer rates on top of the reduction from quadrivalent HPV vaccine programs. Nevertheless, when taking into consideration
the percentage of neoplasias caused by the 5 additional HPV types and the effectiveness of the 9-valent vaccine at preventing these infections, an effective vaccination program with the 9-valent vaccine would likely lead to further reduction of HPV-related cancers.

Conclusion
Available evidence has demonstrated the efficacy and safety of the 9-valent HPV vaccine. The vaccine has the potential to prevent most cervical cancers and further reduce the incidences of other HPV-associated cancers in males and females. Depending on the cost per dose, the 9-valent vaccine could prove to be more cost-effective than the current quadrivalent vaccine in female-only vaccination programs. With these factors in mind, family physicians should recommend to patients the 9-valent vaccine over the current quadrivalent vaccine. Physicians can also improve overall population health by advocating the use of the 9-valent vaccine in provincial vaccination programs. While the 9-valent vaccine is also effective in males, the cost-effectiveness of vaccinating the Canadian male population should be further examined before recommendations can be made for the inclusion of males in vaccination programs.

Mr Yang is a medical student at the Michael G. DeGroote School of Medicine at McMaster University in Hamilton, Ont. Dr Bracken is Associate Professor in the Department of Family Medicine at McMaster University.

Competing interests
None declared.

Correspondence
Mr David Yi Yang; e-mail david.yang@medportal.ca

References