

Position Statement

Human papillomavirus vaccine for children and adolescents

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Abstract

Human papillomavirus (HPV) is known to cause genital warts, cervical cancer, penile cancer, anal cancer and oropharyngeal cancer. In North America, the lifetime cumulative incidence of HPV infection is estimated at more than 70% for all HPV types combined. A safe and effective vaccine against nine HPV types is available. HPV vaccine should be administered routinely to all girls and boys between the ages of 9 and 13 years of age. All youth who have not received the vaccine in a routine program should receive the vaccine in a ‘catch-up’ program. Physicians caring for children and youth should advocate for funding and implementation of universal HPV vaccine programs.

Keywords: HPV; Vaccine

Vaccines for the prevention of human papillomavirus (HPV) infection have been approved in Canada since 2006. Between 2007 and 2010, all provinces and territories implemented publicly funded routine HPV immunization programs for girls with quadrivalent vaccine (types 6, 11, 16 and 18). Programs are all administered by public health in school-based programs to children in specific grades ranging between grades 4 and 8, depending on the province or territory. Some provinces have implemented time-limited catch-up programs for older girls. In February 2010, the quadrivalent HPV vaccine (HPV-4) was approved for use in Canada for males 9 to 26 years of age. In January 2012, HPV-4 was recommended for routine use in boys by the National Advisory Committee on Immunization (1). By summer 2017, eight provinces had announced HPV programs that included males (up-to-date provincial/territorial vaccine schedules can be found at: <http://healthycanadians.gc.ca/healthy-living-vie-saine/immunization-immunisation/schedule-calendrier/infants-children-vaccination-enfants-nourrissons-eng.php>). In 2015, a nonavalent (nine valent) HPV vaccine (HPV-9) was also authorized for use in Canada and, in 2016, the National Advisory Committee on Immunization published recommendations for its use. This position statement updates

previous Canadian Paediatric Society recommendations on the use of HPV vaccine in children and adolescents (2).

HPV INFECTION AND DISEASE

HPV is a double-stranded DNA virus. It has more than 100 types, of which approximately 40 can infect the human genital tract. HPV infections are transmitted sexually by direct epithelial-to-epithelial contact. Rarely, the virus is transmitted vertically to an infant exposed in the maternal genital tract. Exposure can lead to a rare but serious condition known as ‘juvenile-onset recurrent respiratory papillomatosis’. Head and neck infections also occur in adults, mostly through oral genital contact. Clinical manifestations of HPV infection include asymptomatic infection (by far the most common), warts and malignancies. Persistent infection with a high-risk HPV type is the main cause of cervical cancer and also causes cancers of the vulva, vagina, penis, anus, mouth and oropharynx. Low-risk HPV types are associated with the development of nonmalignant cervical dysplasia and anal/genital warts.

The presence of HPV is necessary for the development of cervical cancer but infection must persist for years before lesions become malignant. In the prevaccine era, HPV 16 and HPV 18

were associated with about 70% of squamous cell carcinomas, 86% of adenocarcinoma of the cervix, 90% of anal carcinomas, and approximately 50% of penile cancers and 42.8% of vulvar cancers. The five additional types contained in the HPV-9 vaccine (31, 33, 45, 52 and 58) are estimated to cover an additional 15% to 20% of cervical cancers, 24% of vaginal cancers, 9% of penile and anal cancers, and 2.5% of vulvar cancers. In addition, at least 35% of oropharyngeal cancers are associated with HPV, the majority with HPV 16 and 18 (3). HPV types 6 and 11 are benign and cause 90% of genital warts.

In North America, the lifetime cumulative incidence of HPV infection with at least one serotype is estimated at more than 70%. Without vaccination, it is likely that most sexually active Canadians will have an HPV infection at some point in their lives. The highest prevalence is in young adults 20 to 24 years of age. Because HPV is not a nationally notifiable disease, is usually asymptomatic, and HPV diagnostics are neither widely available nor publically funded, good epidemiological data are lacking. Canadian studies have reported incidence rates of genital warts between 131 to 154 per 100,000 in men and approximately 120 per 100,000 in women. In 2011, the cervical cancer incidence rate in Canada was estimated to be seven cases per 100,000. Annually in Canada, there are approximately 1300 cervical cancer cases and 350 deaths. In 2005, incidences of oropharyngeal and oral cavity cancers among men were 0.54 per 100,000 and 5.2 per 100,000, respectively (4). Women who have sex with HPV-infected males are at higher risk for precancerous lesions and cervical cancer (5).

Risk factors for HPV infection include a higher lifetime number of sexual partners, previous other sexually transmitted infections, history of sexual abuse, early age of first sexual intercourse, partner's number of lifetime sexual partners, tobacco or marijuana use, immune suppression and human immunodeficiency virus (HIV) infection (4). HPV infection and anal warts and cancers are highly prominent among men who have sex with men (MSM), particularly if they are HIV-positive (6).

To be optimally effective in preventing long-term complications from HPV infection, vaccine must be administered before acquisition of the virus. Because infection can occur with the onset of any sexual touching, it is important to vaccinate before first sexual relationships (7). Statistics Canada data from 2005 show 29% of 15- to 17-year-olds had had first sexual intercourse: this number increased to 65% in 18- to 19-year-olds, with large regional variability (8).

There is evidence that girls who are offered or receive HPV vaccine are no more likely to be sexually active than are girls not offered the vaccine. HPV vaccine status does not increase rates of sexually transmitted infections, nor do vaccinated youth engage in earlier or riskier sexual behaviours (9).

HPV VACCINES

There are three approved HPV vaccines in Canada. The vaccine approved most recently is Gardasil 9, the nonavalent vaccine

against HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58, manufactured by Merck Canada (HPV-9). The quadrivalent vaccine (Gardasil or HPV-4) targets HPV 6, 11, 16 and 18. The bivalent (HPV-2) vaccine (Cervarix, manufactured by GlaxoSmithKline) targets HPV 16 and 18. All these vaccines are manufactured using recombinant technology, which produces noninfectious virus-like particles containing protein antigens for each type. HPV vaccines are highly effective in preventing HPV-type-related persistent infection. Because the vaccine prevents infection with the papillomavirus (a necessary first step in cancer development), the cellular dysplasia (intraepithelial neoplasia) that predates invasive cancer does not occur, effectively preventing the development of cancer. If vaccine is administered before exposure to the targeted HPV types, efficacy is close to 100% against type-specific cervical disease.

A randomized trial of HPV-4 vaccine in males demonstrated efficacy against target-type-associated external genital lesions, including genital warts, of 90.4%. Efficacy against persistent vaccine-type-related infection was 70% to 96%. A sub-population of MSM was analyzed and showed an efficacy of 77.5% (95% CI: 39.6 to 93.3) against HPV type 6-, 11-, 16- and 18-related anal intraepithelial neoplasia (10).

Australia introduced a universal publically funded vaccination program for women 12 to 26 years old in 2007. National surveillance for genital warts conducted following this initiative demonstrated that with 65% of women vaccinated, there was a decline of 59% in the diagnosis rates of genital warts in women, accompanied by a 28% drop in diagnosis rates of genital warts in heterosexual men. There was, however, no decrease in genital warts observed in MSM. These data suggest that the vaccination of women may prevent transmission of HPV vaccine types to men (11). There are currently no studies that have directly demonstrated that HPV vaccination of men will prevent transmission of vaccine types to women. However, mathematical models predict that the addition of a routine male HPV program would prevent additional cases of genital warts and cervical cancer among women, based on assumptions about transmission of HPV from men to women (12).

VACCINE SAFETY

As with all vaccines, the most common adverse events from HPV vaccines are pain at the site of vaccination (in 82% to 92% of cases), swelling (24% to 44%) or redness (24% to 48%) (4). In more than 94% of recipients, reactions are mild-to-moderate, resolve over a few days and do not prevent completion of the immunization schedule. Since licensing these vaccines, hundreds of millions of doses have been administered worldwide. Postlicensure safety surveillance data have remained consistent with prelicensure data (13). As with any vaccine, anaphylaxis after HPV vaccine can occur but such cases are rare (14,15). Syncope can occur after immunization and is most common among adolescents and young adults. To prevent syncope, observing HPV

vaccine recipients for 15 minutes after administering a dose is recommended. To date, there has been no published evidence to support any association between HPV vaccines and Guillain-Barré syndrome, autoimmune diseases, stroke, venous thromboembolism, acute disseminated encephalomyelitis, multiple sclerosis or any other serious health condition. Postmarketing surveillance has not shown a higher than expected number of deaths following HPV vaccine administration (15).

SPECIAL POPULATIONS

MSM are known to be at higher risk for infection with HPV 6, 11, 16 and 18 than are heterosexual males. Anal cancers and genital warts have a higher incidence among MSM. As teenagers become aware of and explore their sexual identities, same-sex encounters may not be unusual. Men who eventually identify as MSM may be reluctant to discuss their sexual practices with a health care provider, particularly at a young age. They may be worried about issues of confidentiality or judgment. For these reasons, the best strategy for protecting MSM against HPV-related diseases is a universal male vaccination program that does not depend on self-reporting to health care providers. Early receipt of HPV vaccine is expected to deliver maximal benefit in the MSM population.

Individuals infected with HIV are known to have a high burden of HPV-associated adverse outcomes. Genital warts are common and difficult to treat in this population. Anal cancers are particularly common in HIV-infected MSM. The HPV-4 vaccine was found to be safe and immunogenic in one small trial in HIV-infected boys and girls. Antibody titres to type 6 and 18 were lower than those observed in aged-matched HIV-uninfected children, but the clinical significance of this finding is not yet known (16).

HPV vaccines are not live and therefore can be administered to immunocompromised patients. Immune response has not been well studied in all of these populations, who may have suboptimal response to vaccine. Nonetheless, because immunocompromised patients are known to be at higher risk for adverse outcomes with HPV infection, they should be offered the vaccine.

SCHEDULE

Originally, all HPV vaccines were studied and administered on a three-dose schedule. There are data to demonstrate noninferior antibody response in children 9 to 14 years of age given a two-dose schedule compared with 15- to 26-year-old women given a three-dose schedule (17,18). The two doses must be given at least 6 months apart. The efficacy and long-term effectiveness of such a two-dose schedule are not yet known. Immunocompromised children and children infected with HIV should get three doses of HPV vaccine. There are no data on the two-dose schedule for individuals older than 15 years of age.

CHOICE OF VACCINE

When considering the health objectives of HPV vaccine, it seems prudent to ensure coverage for both genital warts and HPV-associated malignancies. HPV-9 covers 90% of genital warts and 85% to 90% of anogenital cancers. However, males proportionately derive less benefit from the additional serotypes in HPV-9 compared with females. The additional serotypes are expected to prevent 320 anogenital cancers annually in Canada (300 in females, 20 in males). Less than 1% of head and neck cancers are due to the additional types in HPV-9.

REIMMUNIZATION WITH HPV-9

While not recommended at a population level, individuals who have completed immunization with a different HPV vaccine may wish to take advantage of the added protection offered by the new types in HPV-9. The current recommended catch-up schedule requires administering the full HPV-9 vaccine series on an age-appropriate schedule.

RECOMMENDATIONS

1. HPV-9 vaccine should be administered routinely to all children at 9 to 13 years of age. To increase the likelihood that the vaccine will be administered before the onset of any sexual activity, the vaccine should be given as early as provincial/territorial programmatic issues allow.
2. HPV vaccine should be administered to all unimmunized females and males 13 years of age and older, as a 'catch-up program'. It is recommended that provinces and territories implement a 'once eligible, always eligible' policy, whereby children qualifying for publically funded vaccines would still be eligible at a later date when they did not receive all the recommended age-appropriate doses.
3. A two-dose schedule for children 9 to 14 years of age is recommended. The two doses must be given at least 6 months apart.
4. Data regarding the immunogenicity and efficacy of HPV vaccine in immunocompromised individuals are currently lacking. However, based on expert opinion, such individuals should be offered the vaccine on a three-dose schedule.
5. HPV vaccine can be given simultaneously with all other vaccines provided to adolescents.
6. Physicians caring for children and youth should counsel patients and their parents about the HPV vaccine, and recommend HPV vaccine even when patients are not eligible for publically funded coverage. Prescriptions for the HPV vaccines should be given and the vaccine should be administered to all individuals who choose to be vaccinated.
7. Physicians caring for children and youth should advocate for and support universal funding and implementation of HPV-9 vaccination programs for both sexes, in all provinces and territories.

8. Individuals may wish to be reimmunized with HPV-9, even if they were fully vaccinated with HPV-2 or HPV-4, to gain added protection from the new HPV types in HPV-9 vaccine. The current schedule is two doses, administered at least 6 months apart for healthy children 9 to 14 years of age, and three doses for those aged 15 years and older.

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