Human papillomavirus vaccines: Why the time is right to implement immunization and surveillance programs in Canada

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There has been much debate surrounding the introduction of the human papillomavirus (HPV) vaccine in Canada (1,2). Questions have been raised about the need for the vaccine and concerns about its safety. Further concerns have been raised about the ineligibility of boys for the vaccine, the duration of immunity and the notion that receipt of the HPV vaccine may result in risky sexual practices in teens.

Are these valid concerns and therefore reasons to abandon or delay implementation of the HPV vaccine program in Canada? Vaccine uptake across Canada has varied from 53% in Ontario to around 80% in Atlantic Canada; lower uptake rates have been attributed in part to misconceptions about the vaccine (3). The present commentary seeks to address some of the issues raised, and to put them into the broader context of HPV and cancer prevention as well as surveillance.

Sir Bradford Hill, a well-known British epidemiologist stated that "all scientific work is incomplete…" and "does not confer upon us a freedom to ignore the knowledge we already have, or postpone the action that it appears to demand at a given time" (4). With regard to HPV, public health experts wish to make recommendations now because more than 30 Canadian women die of cervical cancer every month (5). Under the 'precautionary principle', which advocates decision-making to minimize any substantive risk to human health or the environment even in the absence of complete evidence, current knowledge clearly supports implementation of the HPV vaccine programs without further delay (6).

First, it is important to recognize that HPV infection is common; Canadian studies (7) report a prevalence range of 10% to 30%. Prevalence rates vary by age, geographical area and ethnicity; 20% to 30% of infected persons are infected with multiple HPV types. Males and females are equally likely to have HPV infection. Most acquire infection within two to five years of becoming sexually active, and then clear the infection spontaneously within two years (7). HPV infection can be acquired from the first sexual partner (8). This fact highlights the potential benefit of the use of the preventive vaccine before sexual debut (9).

The link between oncogenic strains of HPV and cervical and other types of cancers has been confirmed. It is estimated that HPV types 16 and 18 cause approximately 70% of cervical cancer (7). Persistent HPV infection induces the development of precancerous lesions, usually after decades. Unfortunately, there are no readily available diagnostic means to determine who will remain persistently infected and who will clear the infection. While cervical cancer incidence and mortality rates have declined for decades in jurisdictions such as Canada because of access to cervical cancer screening, screening participation rates have plateaued over the past several decades. It is difficult to ensure that the most vulnerable groups of women have access to screening.

In Canada in 2007, cervical cancer was estimated to be the 13th most common cancer in females, with 1350 new diagnoses and 390 deaths (5). While the prognosis of cervical cancer is reasonably good if the diagnosis is made early, survivors may develop second cancers at sites adjacent to the cervix (10). Second cancer diagnoses further compromise quality of life and jeopardize survival. In addition to those affected by cervical cancer, there are thousands of Canadian women who face the consequences – psychosocial and physical – that are associated with abnormal Pap test results. While cervical cancer screening has demonstrated success, the success is incomplete, particularly because at least 50% of women diagnosed with cancer of the cervix have seldom or never been screened (11,12). Primary prevention holds further promise to prevent persistent HPV infections that are the necessary cause of cervical cancer.

Genital warts, 90% of which are caused by HPV types 6 and 11, are estimated to affect one in 10 Canadians at some point in their lives (13). While genital warts do not lead to cancer, they are associated with considerable discomfort, embarrassment and multiple relapses. Treatment may be painful, may require many months of repeat physician visits and is noncurative.

The statement (7) by the National Advisory Committee on Immunization summarizes the available solid scientific data showing the efficacy of vaccine in preventing HPV infection with vaccine-specific types and also precancerous lesions of the cervix. The vaccine is currently licensed only in females nine to 26 years of age because this is the age group and sex among whom studies have been completed to date (7). Preliminary efficacy data in females up to 45 years of age have recently been presented (14). The results of studies in males are expected in the near future (7). Available data of quadrivalent vaccine efficacy in males nine to 15 years of age demonstrates similar immunogenicity and safety as in females (15,16).

Many scientific, public health and medical expert groups have reviewed the scientific evidence, and are in favour of HPV vaccine (17,18). The vaccine is now available in many countries through publicly funded programs (17).

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Much concern has been raised about potential adverse events. The vaccine does not contain mercury or the virus. Non-life-threatening side effects such as pain, swelling and redness at the injection site are the most common adverse events. In the vaccine trials (7) of more than 21,000 females, there was no difference in serious complications between the vaccine and placebo arms of the trials. As of January 31, 2008, seven confirmed and one probable case of Guillain-Barré syndrome (GBS) had been reported (with 15 reports pending investigation) through postmarketing surveillance in the United States, following distribution of more than 12 million doses of the HPV vaccine (19). According to the Centers for Disease Control and Prevention, this frequency of GBS events following the HPV vaccine is no higher than would be expected by chance alone in the general population who have not received the HPV vaccine. Further investigation is ongoing to determine whether there is an association between GBS and the simultaneous administration of HPV and a quadrivalent meningococcoccal vaccine (19). As of January 8, 2008, the Public Health Agency of Canada received 145 reports of adverse events, none of which included death or GBS (20). As with all new vaccines, it is important to continue postlicensure surveillance of any unexpected, rare adverse events that may arise because millions of doses are used for an increasingly long period of time. Both the United States and Canada have national surveillance systems to monitor vaccine safety after licensing of vaccines (19,21). Because these are passive surveillance systems, the numbers reported may be an underestimate of all adverse events related to vaccines.

Concerns have also been raised about the duration of immunity with the currently available HPV vaccines. Existing data from phase 2 trials (7) show excellent response at five years postimmunization, with antibody titres far exceeding those acquired with natural immunity. Harper et al (22) demonstrated that peak responses occur one month after the third vaccine, plateau at approximately 18 months and remain relatively stable at 4.5 years of follow-up, thereby supporting the theory that long-term sustained protection is likely. With the large sample size required to reach statistical power and the decades needed for the disease progression, it will be many years before the impact of the vaccine on cervical cancer incidence at the population level will be detectable. The efficacy of the vaccine in preventing HPV infection and precancerous lesions has been demonstrated and it, therefore, makes biological and epidemiological sense that prevention of cancer will be the expected result. Information about the duration of immune response following immunization is often lacking at the outset of a new vaccine program and is not unique to the HPV vaccine. Continued surveillance and research is underway in large study cohorts regarding the duration of vaccine-conferred protection and the need for booster shots (20,23). If a booster dose is required for adults, uptake rates will likely be lower and less complete compared with school-based programs. Such an approach would also add to the complexity of cervical cancer screening programs.

Approximately 27% of women in the quadrivalent vaccine trials (23) had evidence of infection with one or more of the four vaccine-related genotypes at the start of the trial. Given that this vaccine is a preventive vaccine, it is only effective in preventing infection against genotypes to which the individual is naive. This protection may be shown to be better in the long-term because the vaccines could reduce reinfections with the same genotype.

While this is an expensive vaccine (currently over $400 for a three-dose course), analyses have confirmed the vaccine's cost-effectiveness (24). Sensitivity analyses conclude that the vaccine is most cost-effective when provided at younger ages. The predicted costs per quality-adjusted life year are between US$14,583 and US$32,028, depending on what parameters were included in the models. When used as a measure of health outcome, a cost per quality-adjusted life year of US$50,000 or less per life-year saved is considered a cost-effective program. In the Canadian context, and assuming lifelong immunity with the vaccine, modelling has predicted that eight girls would need to be vaccinated to avoid one case of genital warts, 324 girls to avoid one case of cervical cancer and 729 girls to avoid one death from cervical cancer (25). In the model by Brisson et al (24), it was demonstrated that if a booster dose is needed, administration of the HPV vaccine would still be cost-effective. It is important to note that prevention of other cancers and HPV-associated warts have not been included in most economic analyses. In addition, most cost-effectiveness studies have assumed no change in cervical cancer screening recommendations.

Perhaps the most contentious claim is that implementing a HPV vaccine program will precipitate promiscuity or earlier sexual debut. Concerns about sexual behavioural disinhibition are based on assumptions that perceptions of HPV risk protect adolescents from exposure to HPV and that fear of HPV is a motivation for safer sex and/or abstinence (26). Many factors are associated with initiation of sexual activity in adolescents, but fear of a sexually transmitted infection is not a major reason for abstinence. It is unlikely that receiving the vaccine itself will have any negative impact on sexual behaviour when proper information is provided (26-28). In fact, the counter argument may be made that with renewed interest in adolescent sexual education due to HPV vaccine, incorporating HPV education into comprehensive sexual education may in fact result in less risky sexual behaviour (29).

Another important concern is a possible decline in cervical cancer screening participation after introducing the vaccine. HPV immunization (primary prevention) is complementary to screening (secondary prevention), and does not replace cervical cancer screening. There are several reasons why cervical cancer screening must continue in females regardless of HPV immunization status. First, the vaccine does not protect against all HPV types that cause cervical cancer; screening is necessary to detect precancerous lesions caused by nonvaccine HPV types. Second, some women may not receive all three doses or may not receive them at the correct intervals; thereby, the full benefit of immunization is not realized (7). Ongoing efforts to achieve this goal include public and provider education combined with continued monitoring of screening participation.

With the introduction of HPV vaccine, a surveillance mechanism is essential to prospectively track a number of indicators to facilitate evaluation of the vaccine program. Because HPV is not a reportable infection in North America, an alternate surveillance mechanism will be required. Linkage of existing immunization, screening and cancer registry databases are critical to enable evaluation of the long-term vaccine effectiveness, and uptake and impact of vaccine and screening programs. Some of the required aspects for surveillance may include assessment of 'real world' vaccine effectiveness;

baseline data on HPV prevalence; ongoing surveillance to monitor for possible vaccine type mismatch and replacement with nonvaccine HPV types over time; ongoing monitoring of adverse events in vaccine recipients; monitoring cervical cancer screening participation rates after introduction of the HPV vaccine; and monitoring knowledge, attitude and sexual behaviours after implementation of HPV immunization programs.

CONCLUSION

The HPV vaccine is arguably one of the most significant cancer prevention and public health breakthroughs of our time. Indeed, our youth are not guinea pigs, but are entitled to benefit from a vaccine with the potential to reduce the full burden of disease resulting from this common infection. Now is the time to examine how best to use current and future HPV vaccines to benefit Canadians, correct misconceptions and monitor vaccine effectiveness and safety. Public health strives to ensure that all ethnocultural and socioeconomic groups have equal access to cervical screening and this preventive vaccine. Strategies to maximize adherence are required, such as coadministration with other existing vaccines; educating providers, parents and youth; and reinforcing the need for continued cervical cancer screening even after immunization. Ongoing research and development of comprehensive surveillance and monitoring mechanisms will inform future cervical cancer screening guidelines, campaigns to prevent sexually transmitted infections, HPV vaccine initiatives and future vaccine trials.

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