The Human Papillomavirus Vaccine

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The Human Papillomavirus Vaccine
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## CONTENTS

1. INTRODUCTION....................................................................................................... 1
2. HUMAN PAPILLOMAVIRUS.................................................................................. 1
3. HPV VACCINE ...................................................................................................... 1
4. EFFICACY AND SAFETY CONCERNS .............................................................. 2
   4.1 Efficacy.......................................................................................................... 2
   4.2 Safety............................................................................................................ 3
5. PUBLICLY FUNDED HPV IMMUNIZATION PROGRAMS .................................... 4
6. OTHER CONCERNS ............................................................................................ 5
7. CONCLUSION ..................................................................................................... 6
THE HUMAN PAPILLOMAVIRUS VACCINE

1 INTRODUCTION

In July 2006, Health Canada approved GARDASIL®,¹ a vaccine that protects against some strains of the virus known as human papillomavirus (HPV), which are responsible for the vast majority of cervical cancer cases.² It is the first approved vaccine to protect against cancer; however, its approval and subsequent funding for public immunization programs have been met with both accolades and criticisms. This paper provides an overview of the virus, the vaccine, its efficacy and safety, and a discussion of publicly funded HPV immunization programs.

2 HUMAN PAPILLOMAVIRUS³

HPV is a prevalent virus that is transmitted through sexual contact. In fact, the Public Health Agency of Canada (PHAC) indicates that HPV is the most prevalent sexually transmitted infection in Canada. More than 100 HPV types are described in scientific literature and at least 40 of these strains are able to infect the genital tract. As many as 75% of sexually active Canadians, both male and female, will become infected with HPV at some point over their lifetime. HPV prevalence is highest during young adulthood and declines over time. This is because most HPV infections are transient, and healthy individuals can often eliminate the virus spontaneously with few or no symptoms. A Statement on the HPV vaccine issued in 2007 by Canada’s National Advisory Committee on Immunization (NACI), which makes recommendations on the use of all immunizations, indicates that over half of all infections are cleared within a year, although this figure varies depending on the specific HPV strain in question. A 2007 commentary in the Canadian Medical Association Journal (CMAJ) suggested that spontaneous clearance rates may even be higher, citing values of 70% of infections being cleared within a year, and as much as 90% possibly being eliminated within two years.⁴

However, a persistent infection can cause disease and there is no treatment to clear the virus, only treatment for the conditions it may produce. In particular, HPV types 16 and 18 are responsible for 70% of cervical cancers, and types 6 and 11 may account for up to 90% of cases of genital warts.⁵ Rarely, other conditions can also develop due to persistent HPV infection; these include benign and malignant disease or lesions of the penis, anus, vulva, vagina, head and neck, and warts in the upper respiratory tract.⁶ Therefore, even women who have been immunized must continue to be screened for these conditions, particularly with Pap tests, because other strains of the virus may also cause these complications.

3 HPV VACCINE

Health Canada approved GARDASIL® in July 2006 for use in girls and women aged 9–26 years. GARDASIL® is a quadrivalent vaccine, meaning that it is specific to four different types of virus — in this case, HPV types 6, 11, 16 and 18. The vaccine
THE HUMAN PAPILLOMAVIRUS VACCINE

does not contain the complete, intact virus; instead, it is composed of each of the four types’ main proteins, called capsid proteins. The gene for these proteins is inserted into yeast (Saccharomyces cerevisiae) DNA, which then expresses the viral proteins. These products are then separated, purified and combined with the necessary substances (adjuvant, sodium chloride, water, etc.). The vaccine contains no preservative. It is administered as a series of three injections over a six-month period. In February 2010, Health Canada approved another HPV vaccine called Cervarix™,7 this is a bivalent vaccine against HPV types 16 and 18.8

Recommendations on the use of approved vaccines for humans are prepared by NACI, which is made up of experts in the fields of pediatrics, infectious diseases, immunology, medical microbiology, internal medicine and public health. The Committee reports to the Chief Public Health Officer, who heads PHAC and reports to the federal Minister of Health. All recommendations made by NACI are published in the Canadian Immunization Guide, which is updated approximately every four years. NACI is currently reviewing GARDASIL® with respect to whether or not it should be recommended for use in boys and men. In addition, NACI is reviewing Cervarix™ following its recent Health Canada approval.9 Additional statements and updates are published in the Canada Communicable Disease Report, which is issued weekly.

4 EFFICACY AND SAFETY CONCERNS

By approving the HPV vaccine, Health Canada, like the Food and Drug Administration (FDA) in the United States and the European Medicines Agency in the European Union, has declared it to be effective and safe. Canada’s NACI reported on its analysis of the available efficacy and safety data in its February 2007 Statement on Human Papillomavirus Vaccine.10

4.1 EFFICACY

The vaccine’s efficacy was evaluated through four clinical trials involving women between the ages of 16 and 26. In all, the trials included over 21,400 individuals (mostly women, but some men as well) randomly distributed to be in either the vaccine or placebo group. At a three-year follow-up to the triple-dose vaccination, GARDASIL® was found to be 89% effective in preventing persistent HPV 6, 11, 16 and 18.

The trials also examined the duration of protection offered by the vaccine. A subset of 241 women from one of the first clinical trials was followed for 60 months, at which time their blood was tested for the presence of the antibodies to the four viral proteins. The data showed that the vaccine’s efficacy was sustained and there was no evidence of waning immunity – that is, the antibody levels remained high. More specifically, it was noted that, following a peak in antibody levels at around one month following the third dose of vaccine, antibody concentration decreased over time to plateau after an additional 17 months and remain stable for the remainder of the 60 months. Researchers continue to monitor individuals in order to identify when
immunity begins to decline. PHAC indicates that successful vaccination programs are routinely implemented without knowing at the outset the long-term efficacy data.

Finally, the clinical trials considered the efficacy of the vaccine in individuals who have already been exposed to HPV. Subjects were tested prior to vaccination for the presence of HPV 6, 11, 16 or 18. If they tested positive for any of these strains, the subjects remained in the trial but the vaccine’s efficacy was measured only against those strains to which the subjects had not tested positive. NACI recommends that sexually active women get vaccinated, even if they may have been exposed to HPV. (Screening for HPV status is not readily available, and is not performed routinely prior to vaccination with GARDASIL®.) The Advisory Committee suggests that it is highly unlikely that an individual will have been infected with all four strains of HPV; therefore, the vaccine would still have some benefit. NACI emphasizes that there is no evidence that the vaccine can provide protection against an existing infection or have any therapeutic effect on existing cervical lesions resulting from it. The Committee recommends that these limitations be clearly explained when the vaccine is administered to sexually active women.

The clinical trials have been criticized because they did not include girls between 9 and 15 years of age, even though the vaccine is approved for females aged 9–26. However, as this younger age group is less sexually active, the participants would have been less likely to be exposed to the virus during the course of the studies, and therefore the vaccine’s efficacy would not have been efficiently measured. Instead, investigators studied immunogenicity in this younger group (immunogenicity is the ability of a substance foreign to the body to induce an immune response, thereby prompting the production of antibodies). Investigators made the assumption that if the vaccine were successful in causing the body’s immune system to produce antibodies to it, then it would probably also be effective. Trials were conducted that included females aged 16–26 as well as females aged 9–15. In both of these groups, seroconversion was close to 100%, meaning that essentially all of the individuals vaccinated against HPV 6, 11, 16 and 18 produced antibodies against each of these viruses.

As of November 2011, no studies or reports had yet challenged the efficacy of GARDASIL® and Cervarix™ since the two HPV vaccines were approved.

4.2 SAFETY

The clinical trials that examined the vaccine’s efficacy also measured its safety. The findings were analyzed by NACI and discussed in its 2007 Statement on the HPV vaccine. It was found that the vaccine was generally well tolerated and that most reported adverse events were not related to the vaccine, since the rate of adverse event reporting was not statistically different between the vaccine and placebo groups. Further, NACI stated that it found “no evidence that vaccination resulted in allergic reactions or other immune-mediated diseases.” During the course of these trials involving over 21,400 people, there were 17 deaths – 10 in the vaccine group and 7 in the placebo group. These deaths were reportedly due to trauma, suicide, pulmonary embolus, infection, cancer, a complication from a caesarean section, and a cardiac arrhythmia.
Between June 2006 (when the vaccine was approved) and 22 June 2011, 68 deaths were reported within the United States following vaccination with GARDASIL® to the Centers for Disease Control and Prevention (CDC). Only 32 of these could be followed up, as insufficient information was available on the remaining 36 deaths. Nevertheless, as with previous reports on GARDASIL® safety issued through the U.S. Vaccine Adverse Event Reporting System (VAERS), the CDC reported that there was no common pattern between the deaths. This suggested that they were not caused by the vaccine; in fact, some deaths were confirmed as unrelated to the vaccine. It noted that in the clinical trials there had been 10 reported deaths in the vaccine group (sample size 11,778) but also 7 in the placebo group (sample size 9,686), and the deaths were not considered to be vaccine-related. If there were a causal link between vaccination and death, then the number of reported deaths would have been expected to be much higher given that 16 million doses of vaccine had been administered over the initial two-year period.

In June 2008, the U.S. FDA issued a decision that required changes to the package insert for GARDASIL®, to reflect reports received from post-market surveillance. The “adverse reaction” section of the package insert now includes arthralgia, myalgia, asthenia, fatigue, and malaise. This decision was in response to 9,749 reports of adverse reactions to GARDASIL® that had been submitted to VAERS between June 2006 and June 2008. Of these reports, the majority pertained to common reactions to injection, such as pain at the injection site and local swelling. Fewer than 7% of reports reflected serious adverse events, and according to the CDC, which is responsible for monitoring post-market vaccine safety under VAERS, this is about half the rate of serious adverse events for other vaccines. As of June 2008, serious adverse events included 42 reports of Guillain-Barré Syndrome (GBS) within the United States, of which only 13 had been confirmed. (GBS is an autoimmune disease that attacks the nervous system and results in weakness and sometimes partial paralysis. Most people recover from this condition; however, recovery can take anywhere from weeks to years.) Of the confirmed GBS cases, 5 reported vaccination with another vaccine at the same time as GARDASIL®. Of the remaining 29 reports, 8 did not meet the case definition for GBS, 1 had symptoms of GBS prior to vaccination, 11 remained unconfirmed reports, and 9 were pending additional follow-up. The CDC reported that the number of reports of GBS received by VAERS was within the range that could be expected to occur by chance alone, given the incidence of GBS during the second decade of life.

In Canada, PHAC indicates that as of 30 September 2011, it had received a total of 603 reports of adverse events relating to GARDASIL®. As in other jurisdictions, these adverse reactions were largely minor complaints such as injection site irritations. There were, however, 22 hospitalizations and one reported death following HPV immunization. Still, PHAC reported that there are no worrisome trends or patterns of adverse events linked to the HPV vaccine.

5 PUBLICLY FUNDED HPV IMMUNIZATION PROGRAMS

Federal Budget 2007 provided $300 million to provincial and territorial governments in support of HPV immunization programs. The budget put the funds into a third-party
trust whereby provinces and territories could draw down funding, as required and on a per capita basis, over the subsequent three years. According to the Canadian Immunization Committee, the HPV Vaccine Trust was “intended to support the purchase of the HPV vaccine by the provinces and territories” but there was “flexibility provided in the use of a trust mechanism” such that provinces and territories could use the money as appropriate within their jurisdictions. This is not the first example of such a funding formula. Budget 2004 also provided $300 million for a “national immunization strategy that would support the introduction of new and recommended childhood and adolescent vaccines.” These funds were also paid into a third-party trust and allocated on a per capita basis over the subsequent three years, with flexibility for the provinces and territories to draw down funds as required at any time.

Information from PHAC indicates that publicly funded immunization programs for GARDASIL® have been established in all provinces and territories. All programs offer immunization to girls in three doses as recommended by NACI, and vaccinations are provided within the school setting by local public health officials.

Other jurisdictions also offer publicly funded immunization programs for GARDASIL®. For example, Australia administers GARDASIL® under its National Immunization Program, which covers several other vaccinations as well. Under this program, GARDASIL® is administered within a school setting to girls between the ages of 12 and 18, or by a physician within an office setting to women between the ages of 19 and 26. In the United Kingdom, where there is also publicly funded immunization, the vaccine has been offered every year since September 2008 to girls aged 12–13 years. A three-year catch-up program was offered at that time to girls aged 14–17 years.

6 OTHER CONCERNS

In addition to the efficacy and safety concerns that have already been reviewed, other questions have been raised about the need to implement a nationwide, publicly funded program. The CMAJ commentary mentioned earlier discusses several matters that the authors feel may not have been given adequate consideration before funding was provided for vaccination programs in all provinces and territories. The authors first point to the relatively low incidence of cervical cancer in Canada (it is the 11th most frequent cancer in women) and its low mortality rate (it is the 13th most common cause of cancer-related deaths, accounting for about 400 deaths per year). They also note that both the incidence of cervical cancer and the mortality rate from it have been declining for several years. As cervical cancer is a disease that progresses slowly, they suggest that the mortality rate could be further reduced by improving access to proper screening. They also point to the high cost of the vaccine and state that the cost-effectiveness analyses needed to evaluate the expense are lacking.

The NACI Statement highlights the need for additional research to address knowledge and infrastructure gaps. Areas for further research include efficient
delivery of the vaccination program, costs of program delivery, effectiveness of a two-dose schedule, effect on cervical screening programs, means of promoting the vaccine, and the effect of co-administering it with another vaccine.

As research findings are published, this vaccine will become more thoroughly understood. As an example, in September 2008 the CMAJ published an article on the vaccine’s safety, based on observations of the Australian immunization program. The article indicates that in the Australian population there was an observed rate of anaphylactic reaction to the vaccine of 2.6 events per 100,000 doses, with no cases of anaphylactic shock. This rate was said to be “significantly higher” (about 20 times) than that observed in other school-based vaccines, but still very low. The basis for the increased allergic reaction has not yet been identified, but the authors hypothesize that it could be due to prior exposure to HPV or to sensitization from yeast proteins in the hepatitis B vaccine, which is part of the childhood immunization regime, often given a year or two prior to the HPV vaccine. This higher rate of anaphylaxis has not been noted in either the U.S. or Canadian adverse reaction databases, and the authors of the study note that their findings need to be reinforced, or refuted, by further study. There is no suggestion in the article that the vaccine is unsafe.

7 CONCLUSION

Reaction to the HPV vaccine has been mixed. While some welcome the first vaccine to help prevent cancer, others have maintained that there are insufficient safety data to justify implementing large-scale, publicly funded immunization programs aimed at such a young age group. Some critics have also questioned the need for a nationwide vaccination program given the relatively low incidence of, and mortality rate from, cervical cancer.

With regard to the vaccine’s safety, data gathered during the five years since it was approved appear to indicate that the prevalence of adverse reactions to it is no different from that observed with other vaccines. PHAC has indicated the need to remain vigilant in gathering and following up on adverse reaction reports and to continue with research on the vaccine’s safety so that reliable guidelines can be established, should booster immunizations become recommended.

NOTES

1. GARDASIL® is a registered trademark of Merck & Co., Inc.
3. Background information about HPV was largely obtained from the Public Health Agency of Canada [PHAC], “The FACTS on the Safety and Effectiveness of HPV Vaccine.”


6. A more detailed discussion of the conditions associated with persistent HPV infection is available in NACI (2007).

7. Cervarix™ is a registered trademark of GlaxoSmithKline, Inc.


10. For a detailed assessment of HPV infection, HPV epidemiology, epidemiology of diseases caused by HPV, and an analysis of the literature on the vaccine’s efficacy and safety, see NACI (2007).


12. Ibid.

13. PHAC, “The FACTS on the Safety and Effectiveness of HPV Vaccine.”


17. PHAC, “The FACTS on the Safety and Effectiveness of HPV Vaccine.”

