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THE HUMAN PAPILLOMAVIRUS VACCINE

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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.

HUMAN PAPILLOMAVIRUS[3]

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 the scientific literature and at least 40 of these strains are able to infect the genital tract. As much 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

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(1) Gardasil is a registered trademark of Merck & Co., Inc.

(2) National Advisory Committee on Immunization [NACI], *Statement on Human Papillomavirus Vaccine*, published in the *Canada Communicable Disease Report*, Vol. 33, 15 February 2007, p. 2, http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07vol33/acs-02/index_e.html. According to the Canadian Immunization Committee, HPV is present in 99.7% of cervical cancer cases; see *Recommendations on a Human Papillomavirus Immunization Program*, December 2007, p. 4, http://www.phac-aspc.gc.ca/publicat/2008/papillomavirus-papillome/papillomavirus-papillome-index-eng.php.

(3) Background information about HPV was largely obtained from the Public Health Agency of Canada website at http://www.phac-aspc.gc.ca/std-mts/hpv-vph/fact-faits-eng.php.

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 recent commentary in the *Canadian Medical Association Journal* (CMAJ) suggests that spontaneous clearance rates may even be higher, citing values of 70% of infections being cleared within a year, while as much as 90% may be 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.

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 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. According to the PHAC website, as of November 2007 Health Canada was considering

(4) Abby Lippman et al., "Human papillomavirus, vaccines and women's health: questions and cautions," *Canadian Medical Association Journal*, Vol. 177, No. 5, August 2007, pp. 484–87.

(5) NACI (2007), pp. 2–3.

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

another HPV vaccine called Cervarix™ for approval; this is a bivalent vaccine against HPV types 16 and 18.(7)

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 every four years.(8) Additional statements and updates are published in the *Canada Communicable Disease Report*, which appears several times a year.

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*.(9)

A. 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

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(7) Public Health Agency of Canada, "Literature Review on HPV 6, 11, 16 and 18: Disease and Vaccine Characteristics: Canada," 9 November 2007, http://www.phac-aspc.gc.ca/bid-bmi/dsd-dsm/nb-ab/2007/nb4507-eng.php (accessed 19 June 2008).

(8) *Canadian Immunization Guide*, http://www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php.

(9) The NACI Statement provides 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.

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[(10)] in this younger group and made the assumption that if the vaccine were successful in seroconverting[(11)] in these individuals, then it would probably also be efficacious. Trials were conducted that

(10) Immunogenicity refers to the ability of an antigen to induce an immune response, thereby prompting the production of antibodies. ("Antigen" is a contraction of the words "antibody generating.")

(11) Seroconversion refers to the production of antibodies to an antigen, either through natural infection or through immunization.

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.

B. 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.

There have been reports of deaths in other countries since Gardasil was put on the market. The European Medicines Agency issued a statement on 24 January 2008 concerning the deaths in Europe of two young women who had received the vaccine. The Agency indicated that "[n]o causal relationship has been established between the deaths of the young women and the administration of Gardasil." No cause of death was identified in either case, and the Agency reaffirmed that the benefits of the vaccine outweigh the risks.(12)

Between June 2006 (when the vaccine was approved) and 31 August 2008, 27 deaths within the United States following vaccination with Gardasil were reported to the Centers for Disease Control and Prevention (CDC).(13) Only 20 of these could be followed up, as insufficient information was available on the others. Nevertheless, as with previous reports on Gardasil safety issued through the US Vaccine Adverse Event Reporting System (VAERS), the CDC reported that there was no common pattern between the deaths, suggesting that they were not caused by the vaccine. It noted that in the clinical trials there had been 10 reported deaths in

(12) The European Medecines Agency issued the statement following reports questioning the vaccine's safety; it is available online at http://www.emea.europa.eu/humandocs/PDFs/EPAR/gardasil/Gardasil_press_release.pdf.

(13) Information from the Centers for Disease Control, Vaccine Adverse Event Reporting System website at http://www.cdc.gov/vaccinesafety/vaers/gardasil.htm (accessed 25 August 2008).

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 be expected to be much higher given that 16 million doses of vaccine had been administered over the two-year period.

In June 2008, the US 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 must now include 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. 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 rate of GBS during the second decade of life.(14)

In Canada, PHAC indicates that as of 30 June 2008, it had received a total of 212 reports of adverse events relating to Gardasil, none of which were deaths or cases of GBS. As in other jurisdictions, these adverse reactions were largely minor complaints such as injection site irritations. There were, however, six hospitalizations following HPV immunization. One of these was found to be clearly related to the vaccine; one was found to be possibly related to it; three were found not to be related to it; and one had yet to be reviewed at the time of this publication.(15)

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(14) Ibid.

(15) Public Health Agency of Canada, "The Facts on the Safety and Effectiveness of HPV Vaccine," http://www.phac-aspc.gc.ca/std-mts/hpv-vph/fact-faits_e.html.

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 can draw down funding, as they require and on a per capita basis, over the subsequent three years.(16) According to the Canadian Immunization Committee, the HPV Vaccine Trust is "intended to support the purchase of the HPV vaccine by the provinces and territories" but "[t]here is flexibility provided in the use of a trust mechanism such that provinces and territories can use this money as appropriate within their jurisdictions."(17) 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."(18) 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.

It is unclear whether funding for Gardasil will be extended beyond 2010, but Budget 2007 indicated that the funds were intended to launch the immunization program, suggesting that further costs would not necessarily be covered. Once the duration of Gardasil's protection has been determined, the government may have to decide whether a booster immunization will also be publicly funded.

Information from PHAC indicates that, as of August 2008, publicly funded immunization programs for Gardasil have been established in all of the provinces except Quebec, but in none of the territories. All the participating provinces offer immunization to girls in three doses as recommended by NACI, and vaccinations are provided within the school setting by local public health officials.(19)

Other jurisdictions also offer publicly funded immunization programs for Gardasil. For example, Australia administers Gardasil under its National Immunization

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(16) Government of Canada, *The Budget Plan 2007*, p. 96, http://www.budget.gc.ca/2007/pdf/bp2007e.pdf.

(17) Canadian Immunization Committee (2007), p. 3.

(18) Government of Canada, *The Budget Plan 2004*, ch. 4, p. 101, http://www.fin.gc.ca/budget04/PDF/bp2004e.pdf.

(19) A complete table of provincial and territorial immunization programs is available on the Public Health Agency of Canada's website at http://www.phac-aspc.gc.ca/im/ptimprog-progimpt/table-1_e.html.

Program, which covers several other vaccinations as well. Under this program, Gardasil is administered within the school setting to girls between the ages of 12 and 18, or by a physician within the office setting to women between the ages of 19 and 26.(20) In the United Kingdom, where there is also publicly funded immunization, the vaccine will be offered every year starting in autumn 2008 to girls aged 12–13 years. A three-year catch-up program will also start at that time and will offer the vaccine to girls aged 13–18 years.(21)

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 above 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 Gardasil 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

(20) Information from the Australian Department of Health and Ageing at http://www.health.gov.au/internet/main/publishing.nsf/Content/gardasil_hpv.htm.

(21) Information from the UK National Health Service at http://www.immunisation.nhs.uk/Vaccines/HPV.

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 US 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.(22)

CONCLUSION

Reaction to the new 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 two 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. It is necessary, though, as the Public Health Agency of Canada has indicated, 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 for booster immunizations.

(22) J. Brotherton et al., "Anaphylaxis following quadrivalent human papillomavirus vaccination," *Canadian Medical Association Journal*, Vol. 179, No. 6, September 2008, pp. 525–33.