

## **Gardasil®: The Facts**

### **Questions & Answers in Response to Maclean's Article**

**Q1. Are we not overreacting by implementing provincial HPV vaccination programs? Why do we need Gardasil®?**

**A** GARDASIL® is indicated for the prevention of cervical cancer as well as several other diseases associated with HPV types 6, 11, 16 and 18, such as vulvar and vaginal cancer, genital warts and the precursors to these diseases. Vaccination of young women was 96%-100% effective in preventing infections from the HPV types that account for more than 90 per cent of genital warts, approximately 70 per cent of cervical and anogenital cancers and high-grade pre-cancers, 35 to 50 per cent of low-grade cervical, vaginal and vulvar lesions, and all four types cause abnormal Pap test results.<sup>1</sup>

So far 80 countries, including Canada, have approved Gardasil® on the merits of the scientific data.

While most HPV infections do clear on their own, the burden of HPV disease is still significant. HPV infections annually lead to approximately 400,000 abnormal Pap smear results<sup>2</sup>, 85,000 consultations due to genital warts and 36,000 new cases of genital warts<sup>3</sup>, as well as 1,400 cervical cancer diagnoses and 400 cervical cancer deaths<sup>4</sup>. HPV is also linked to loss of female fertility and premature ovarian failure.<sup>5</sup>

**Q2. Why do we need to immunize young girls?**

**A** The best time to hold public immunization programs is when young girls can take advantage of established immunization infrastructures in the school system. The only way for a vaccine to be effective is to vaccinate prior to exposure to the virus. The use of Gardasil® today will help prevent infections that could, five or ten or twenty years from now, become cervical cancer.

**Q3. How does Merck Frosst explain the complaints on the Vaccine Adverse Event Reporting System, such as death, paralysis, seizures, Guillain-Barré Syndrome and more?**

**A** The clinical trials found no increased number of serious adverse events in girls/women who received vaccine compared with those who received placebo. Before the National Advisory Committee on Immunisation (NACI) recommends any vaccine, it weighs the known and potential benefits against known risks. Like all vaccines, Gardasil® has some side effects, but NACI determined that the benefits outweigh the risks. This is in line with other immunization recommending bodies such as, the American Committee on Immunisation Practice (ACIP).

Since the vaccine has been approved, the most common reports to the Vaccine Adverse Events Reporting System (VAERS) in the U.S. have been local injection site reactions - as was seen in the clinical trials. There were some cases of fainting after vaccination. This has been found with other vaccines administered to adolescents. Many people have a fainting episode at some point in their life and there are many potential causes. General recommendations for all vaccines include a suggestion for a 15 minute post-vaccination waiting period.

Since the vaccine was approved, there have been 13 reports of Guillain-Barre Syndrome (GBS) among persons who received Gardasil®. CDC investigators are in the process of confirming GBS. Of the 13 reports, six individuals received Gardasil® given alone, five received Gardasil® and Menactra®, one received Gardasil®, Menactra®, and Hepatitis A vaccine, and one received Gardasil® and Pneumococcal Polysaccharide Vaccine given within 30 days of one another. Because GBS occurs at a rate of 1-2/100,000 person years during the second decade of life, some cases will occur by coincidence following vaccination (but not due to vaccination). To date the cases of GBS reported through VAERS for Gardasil® are below the expected naturally occurring background rate.

Since the vaccine was licensed, there have been three deaths reported among persons who received Gardasil®: One involving a pulmonary embolism; one involving myocarditis due to influenza A infection; and one from a blood clot. These deaths are being fully investigated. Since more than 5 million doses have been distributed, some deaths will occur coincidentally following vaccination (but not due to vaccination).

**Q4. Critics say the goal of the HPV vaccination program is not clear. Is the goal to eradicate high-risk HPV types or to reduce the number of deaths from cervical cancer?**

**A** Cervical cancer is not the only issue: Gardasil® is indicated for cervical cancer as well as several other diseases associated with HPV types 6, 11, 16 and 18, including vulvar and vaginal cancer, genital warts and the precursors to these diseases. As such, an effective preventative HPV vaccine program combined with on going cervical screening would have the ability to significantly reduce the overall burden of HPV related diseases.

**Q5. Critics question the “real world” efficacy of Gardasil®? How do you respond?**

**A** Gardasil® is extremely effective at preventing disease, but does not alter the course of pre-existing infections. For example, in the FUTURE I trial, none of the 2,261 women receiving Gardasil® who were not already infected with the vaccine HPV types developed an HPV-related disease. And in the FUTURE II trial, 1 of the 5,305 women receiving Gardasil® who were not already infected with the vaccine HPV types developed an HPV-related disease. That’s why it is so important to vaccinate young girls before they come in contact with virus that causes these diseases.

In the overall study populations (real life situations), efficacy increases over time as new infections occur in the placebo group but not in the vaccine group. The fact that we are seeing significant differences between the vaccinated and placebo groups in the overall population analyses after a short three years of follow-up bodes well for the effectiveness of Gardasil® in public programs.

**Q6. Critics also question the duration of efficacy of Gardasil®. Is it really worth it to vaccinate girls at nine if the vaccine is only effective for five or six years?**

**A** Our clinical data shows that Gardasil® is effective for five years and the immune response in girls as young as nine was shown to be strong. And the immune response in nine year old girls was shown to be the strongest. Moreover, there is evidence of strong immune memory, a hallmark for long lasting protection. We continue to follow women in the studies to track longer-term efficacy.

**Q7. Critics say the data available about girls in the 9-13 age group is thin. Why is this the case?**

A The goal of the clinical trials for Gardasil® was to test the vaccine's effectiveness at preventing HPV infections, which are transmitted through sexual activity. Most of the participants in the clinical trials were women aged 16 through 26, the age at which the risk for HPV infection is highest. Studies demonstrating the efficacy of HPV vaccines against disease endpoints in young girls are not feasible given legal and ethical issues regarding evaluations of sexual activity in this population and the relatively low rate of exposure to the virus at this age. Since girls 9-13 are generally not sexually active, Merck Frosst and Health Canada agreed that efficacy findings in 16- to 26-year-olds can be applied to younger adolescents, since the immune response in young girls was higher than in adolescents and adults. This so-called immunogenicity "bridging" is an accepted surrogate for efficacy with most childhood vaccines.<sup>6</sup>

**Q8. Critics say Gardasil® is expensive and that no cost-effectiveness studies have been carried out. How do you respond?**

A There have been extensive cost-effectiveness analyses of HPV vaccines from across the globe, all suggesting substantial reduction in cervical cancer mortalities and represent cost-effective additions to cervical screening<sup>7</sup>. One such cost-effectiveness analysis was conducted by Dr. Marc Brisson, who holds the Canada Research Chair in Mathematical Modeling and Health Economics of Infectious Diseases at Laval University. In it, Canadian age and type specific data for infection, cervical dysplasias and cancer and genital warts was modeled. This study suggests that vaccinating adolescent girls against HPV is likely to be cost-effective under current Pap testing programs in Canada<sup>8</sup>.

**Q9. Could short-term immunity alter the natural history of the infection, such that the disease reappears to a different degree later in life?**

A As outlined in the CMAJ commentary, Lippman et al highlight the importance of the long-term duration of the immune response from a HPV vaccine. This is indeed an important consideration however, at the start of any vaccination program, it is impossible to say whether boosting will be required; that is the role and importance of post-vaccine surveillance. What we do know is that antibody concentrations remain up to 10 to 20 times that found in natural infections for at least 5 years post vaccination. Moreover, there is evidence that the vaccine elicits a strong immune memory, the later being the hallmark for long-term protection.

**Q10. Will the other non-vaccine HPV types become more prevalent? This appears to be the case for invasive pneumococcal disease.**

A The threat that other oncogenic HPV types will replace HPV -16 and -18 is more of a theoretical concern than a barrier to implementing a vaccination program based on the known virology, natural history and epidemiology of HPV. As with evaluating the long-term duration of protection, post-vaccine surveillance will evaluate the theoretical risk for type replacement.

**Q11. Critics contend that HPV vaccination may lead to reductions in safe sex practices and Pap screening rates. How do you respond?**

A There is no reason to believe that Canadians will think that an HPV vaccine will prevent all sexually transmitted diseases. As for Pap tests, Merck Frosst has always promoted a three-pronged approach: education, vaccination and continued Pap tests. In fact, we believe the vaccine has done much to raise awareness about the importance of Pap tests, what they are for and the relation between Pap testing and HPV. In a recent Ipsos-

Reid survey, almost all (98%) Canadian parents knew that the vaccine is not a substitute for regular pap testing and recognized that pap testing for protection against cervical cancer is still necessary, even with the HPV vaccine.

**Q12. Critics question whether we really need an HPV vaccine to prevent cervical cancer, implying that sex education and Pap screening would be enough. How do you respond?**

**A** We must first make it clear that Gardasil® is indicated for cervical cancer as well as several other diseases associated with HPV types 6, 11, 16 and 18, such as vulvar and vaginal cancer, genital warts and the precursors to these diseases.

Despite incredible advances in communication over the last 20 years and the vast improvement of Pap screening programs, HPV infections annually lead to approximately 400,000 abnormal Pap smear results<sup>9</sup>, 85,000 consultations due to genital warts and 36,000 new cases of genital warts<sup>10</sup>, as well as 1,400 cervical cancer diagnoses and 400 cervical cancer deaths<sup>11</sup>. HPV is also linked to loss of female fertility and premature ovarian failure.<sup>12</sup> According to the Society of Obstetricians and Gynaecologists of Canada, the incidence of cervical cancer is also on the rise in Canada.<sup>13</sup>

Merck Frosst therefore believes in a three-pronged approach: education, vaccination and continued Pap tests.

**Q13. Won't HPV vaccination programs miss the most affected groups of women: immigrants, refugees, Aboriginals, the disabled, poor and those living in remote regions?**

**A** Merck Frosst is supportive of a national, three-pronged approach to battling HPV-related diseases: education, vaccination and continued Pap tests. We must execute on these three levels if we wish to reach all women across the country. As with evaluating the long-term duration of protection and the theoretical risk of type replacement, post-vaccine surveillance will evaluate the effective implementation of the vaccine for everyone.

**Q14. Critics claim there is no evidence that Gardasil® reduced cervical cancer cases or deaths. How do you respond?**

**A** For ethical reasons, cervical cancer was not chosen as an endpoint of our clinical studies. Since women who develop pre-cancerous lesions must be treated before cervical cancer develops, national and international health agencies, including the U.S. Food and Drug Administration and the World Health Organization, decided that efficacy against CIN 2/3 (highest grade of pre-cancerous lesions of the cervix and the necessary precursor to cervical cancer) is the most clinically relevant measure of an HPV vaccine's effectiveness against cervical cancer.<sup>14</sup>

**Q15. Experts recommend an HPV vaccine registry. Does Merck Frosst support this idea?**

**A** Absolutely. In fact, as a company, we are already following the long term impact of Gardasil® on the overall incidence of cervical pre-cancers and cancers through the Nordic Cancer Registry program.<sup>15</sup>

**Q16. Isn't it in the best interest of public health to study vaccines beyond clinical trials?**

**A** Merck Frosst, as part of the Merck Company, is conducting several studies to assess long-term safety and duration of efficacy, including post-approval evaluation of 35,000 subjects to evaluate general safety and pregnancy outcomes. A pregnancy registry will further monitor pregnancy outcomes in women who received Gardasil®. In addition, 5,500 subjects from the FUTURE (Females United To Unilaterally Reduce Endo/Ectocervical Disease) II study will be followed throughout their lifetimes. Evaluation of the long-term safety and duration of efficacy of Gardasil® is part of the Nordic Cancer Registry Program, a population-based evaluation of Gardasil® in Nordic countries planning to implement a mandatory HPV vaccine registry. Pap test and biopsy results can be tracked very closely in Scandinavia, where governments require reporting of results by national ID number.<sup>16</sup>

**Q17. Couldn't we save money by giving girls two shots instead of three?**

**A** There is not enough data to answer this question, since practically all the participants in clinical studies completed the three-dose regimen. We are collaborating with the province of British Columbia in their study evaluating the efficacy of a two-dose regimen with Gardasil®.

**Sources:**

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<sup>1</sup> Efficacy of a Prophylactic Quadrivalent Human Papillomavirus (HPV) (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine for Prevention of Cervical Dysplasia and External Genital Lesions (EGL), exposé présenté par C. Sattler à la 45<sup>e</sup> conférence (annuelle) interdisciplinaire sur les agents antimicrobiens et la chimiothérapie (ICAAC), à Washington, DC.

<sup>2</sup> Statement by the Society of Obstetricians and Gynaecologists of Canada (SOGC) on CMAJ Commentary, "Human papillomavirus, vaccines and women's health: questions and cautions". (Accessed on August 14, 2007 at: [http://www.sogc.org/media/guidelines-hpv-commentary\\_e.asp](http://www.sogc.org/media/guidelines-hpv-commentary_e.asp))

<sup>3</sup> Brisson, M et al. The health and economic burden of HPV infection, genital warts, cervical dysplasia and cervical cancer in Canada. Presented at the 7<sup>th</sup> Canadian Immunization Conference (CIC) on December 3, 2006 in Winnipeg.

<sup>4</sup> Public Health Agency of Canada, Cervical Cancer Screening in Canada: 1998 Surveillance Report, Executive Summary. (Accessed at [http://www.phac-aspc.gc.ca/publicat/ccsic-dccuac/exec\\_e.html](http://www.phac-aspc.gc.ca/publicat/ccsic-dccuac/exec_e.html)).

<sup>5</sup> Statement by the Society of Obstetricians and Gynaecologists of Canada (SOGC) on CMAJ Commentary, "Human papillomavirus, vaccines and women's health: questions and cautions". (Accessed on August 14, 2007 at: [http://www.sogc.org/media/guidelines-hpv-commentary\\_e.asp](http://www.sogc.org/media/guidelines-hpv-commentary_e.asp))

<sup>6</sup> Merck & Co. Q&A document developed for the ACIP Meeting and dated June 29, 2006.

<sup>7</sup> Barnabas, R.V., Kulasingam, S.L. Economic Evaluations of Human papillomavirus vaccines, Expert Rev pharmacoeconomics Outcomes Res. 7(3) 2007.

<sup>8</sup> Brisson, M et al., The potential cost-effectiveness of prophylactic human papillomavirus vaccines in Canada, Vaccine 25, 2007, 5399-5408.

<sup>9</sup> Statement by the Society of Obstetricians and Gynaecologists of Canada (SOGC) on CMAJ Commentary, "Human papillomavirus, vaccines and women's health: questions and cautions". (Accessed on August 14, 2007 at: [http://www.sogc.org/media/guidelines-hpv-commentary\\_e.asp](http://www.sogc.org/media/guidelines-hpv-commentary_e.asp))

<sup>10</sup> Brisson, M et al. The health and economic burden of HPV infection, genital warts, cervical dysplasia and cervical cancer in Canada. Presented at the 7<sup>th</sup> Canadian Immunization Conference (CIC) on December 3, 2006 in Winnipeg.

<sup>11</sup> Public Health Agency of Canada, Cervical Cancer Screening in Canada: 1998 Surveillance Report, Executive Summary. (Accessed at [http://www.phac-aspc.gc.ca/publicat/ccsic-dccuac/exec\\_e.html](http://www.phac-aspc.gc.ca/publicat/ccsic-dccuac/exec_e.html)).

<sup>12</sup> Statement by the Society of Obstetricians and Gynaecologists of Canada (SOGC) on CMAJ Commentary, "Human papillomavirus, vaccines and women's health: questions and cautions". (Accessed on August 14, 2007 at: [http://www.sogc.org/media/guidelines-hpv-commentary\\_e.asp](http://www.sogc.org/media/guidelines-hpv-commentary_e.asp))

<sup>13</sup> Statement by the Society of Obstetricians and Gynaecologists of Canada (SOGC) on CMAJ Commentary, "Human papillomavirus, vaccines and women's health: questions and cautions". (Accessed on August 14, 2007 at: [http://www.sogc.org/media/guidelines-hpv-commentary\\_e.asp](http://www.sogc.org/media/guidelines-hpv-commentary_e.asp))

<sup>14</sup> Merck & Co. Q&A document developed for the ACIP Meeting and dated June 29, 2006.

<sup>15</sup> Briefing Document presented to the Vaccines and Related Biological Products Advisory Committee (VRBPAC) of the US FDA on May 18, 2006.

<sup>16</sup> Briefing Document presented to the Vaccines and Related Biological Products Advisory Committee (VRBPAC) of the US FDA on May 18, 2006.