Gardasil® – The New HPV Vaccine: The Right Product, the Right Time? A Commentary

Gardasil® – le nouveau vaccin contre le PVH : s'agit-il du bon produit au bon moment? Commentaire

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Abstract

The federal and provincial governments have undertaken a universal immunization program to protect school-aged girls against cervical cancer using the new human papillomavirus vaccine Gardasil®. While the vaccine appears to be effective and safe, there are a number of important unanswered questions regarding it and the effects of the immunization program. Here we briefly review key literature about the vaccine and then use the Erickson criteria, which offer an evidence basis for decision-making regarding national immunization strategies, to evaluate whether the program is congruent with sound public health policy. Our analysis of the national decision to recommend and fund a vaccination program using Gardasil® raises significant questions about the basis for this program.

Résumé

Les gouvernements fédéral et provinciaux ont entrepris un programme de vaccination universelle, chez les filles d'âge scolaire, pour prévenir le cancer du col de l'utérus à l'aide du nouveau vaccin contre le papillomavirus humain, Gardasil®. Bien qu'il semble efficace et sécuritaire, il existe de nombreuses questions sans réponse quant au vaccin et aux effets du programme de vaccination. Nous examinons brièvement ici la principale littérature au sujet du vaccin et nous employons les critères d'Erickson, qui offrent un cadre pour la prise de décisions en matière de stratégies nationales de vaccination, afin d'évaluer si le programme coïncide ou non avec de solides politiques de santé publique. Notre analyse de la décision nationale visant à recommander et à financer un programme de vaccination utilisant le Gardasil® soulève des questions raisonnables quant aux fondements de ce programme.

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Gardasil®, a new vaccine against human papillomavirus (HPV) designed to prevent cervical cancer, was licensed by Health Canada in July 2006. In February 2007, the National Advisory Committee on Immunization (NACI) recommended that girls aged 9–13 years (i.e., before the onset of sexual intercourse) and women aged 14–26, even if they have had previous Pap smear abnormalities or HPV infections, be immunized. The federal government followed with an announcement of a $300-million allocation to provincially organized immunization programs. The immunization strategy has received the support of the Public Health Agency of Canada (PHAC), the Canadian Paediatric Society and the Society of Obstetricians and Gynaecologists (SOGC). The vaccine is now being provided free of charge to school-aged girls in all provinces and the Yukon Territory.

The Canadian Women's Health Network has advised caution about the program,

and a peer-reviewed paper in the *CMAJ* (Lippman et al. 2007) said that the decision may have been premature. Merck Frosst, the SOGC and the Chief Public Health Officer of Canada have each publicly defended the vaccine program against such criticisms. Was the decision to offer widespread provision of the vaccine sound public policy based on science – the best use of our resources to decrease morbidity and save lives?

Decision-Making in Public Policy

Decision-making in public policy is challenging; scientific evidence of benefit and risk is only part of the equation. Exogenous factors such as crises and economic pressure, ideology and values, and stakeholders, including media and lobby groups, each necessarily play roles in determining health policy. But all these considerations need to be taken into account in a transparent and systematic manner from both the individual and societal perspectives before making a recommendation. Has this been done in the case of the HPV vaccine?

Erickson and colleagues were funded by the Canadian Institutes of Health Research and Health Canada's Subcommittee on Immunization of the Advisory Committee on Population Health to help enhance decision-making on vaccines and to develop more uniform and evidence-based decision-making in the context of a national immunization strategy. Through a modified Delphi process they defined 58 criteria under 13 broad categories including such factors as the burden of disease, vaccine characteristics, immunization strategy, cost-effectiveness, acceptability, feasibility and evaluability of the program, along with equity, ethical, legal and political considerations (Erickson et al. 2005).

PHAC organized a workshop on the HPV vaccine in 2006, explicitly using the Erickson criteria to evaluate the questions that a public health authority might raise when considering establishment of an HPV immunization program (PHAC 2006). The following year NACI concentrated on two elements of the Erickson criteria (burden of disease and vaccine characteristics) in making specific recommendations about using the vaccine (NACI 2007). The criteria have also been used in the decision-making of the Canadian Immunization Committee (CIC 2007).

We recognize that the federal nature of Canada means that the final shape of any vaccination program rests with provincial governments. However, their decisions will be based, at least in part, on what has transpired at the national level where the Erickson criteria were applied. Therefore, in this commentary we use 10 of the 13 Erickson criteria, including the two that were used by NACI, to revisit the national decision to recommend and fund a program to vaccinate school-aged girls with Gardasil®. The three criteria omitted – ethical and legal considerations and conformity of programs – are more appropriately evaluated in individual provincial-level programs.

Our paper is not a systematic review but rather is intended to stimulate debate about health policy. Therefore, we cite representative literature from well-argued commentaries that present important arguments about public health issues as well as original literature to illustrate our points. A more comprehensive evaluation of the material about cervical cancer and vaccination programs is beyond the scope of this article.

Erickson Criteria for Decision-Making on Vaccines

Burden of disease

Cervical cancer is the 11th most common cause of cancer in women, afflicting 1,350 Canadian women and killing 400 annually. Adding HPV vaccination prior to HPV exposure in girls to an ongoing secondary screening campaign (Pap smears) and the promotion of safe sexual practices is being advanced as a way to reduce the burden of disease from cervical cancer, especially in vulnerable groups of women (CIC 2007). These vulnerable groups include immigrant and Aboriginal women and the disabled, each of whom may miss Pap screening for reasons of culture, language, education, poverty and distance from healthcare facilities (NACI 2007). Previous work in the United States and Belgium has linked school vaccination rates to such factors as fathers' socio-economic status, lower educational level, single-parent families and race (Middleman 2004; Vandermeulen et al. 2008). There does not appear to have been any investigation to establish whether a school-based program of the type being instituted in Canada might miss people from the same demographic who currently have low cervical screening rates, questions related to one of the Erickson criteria. In a survey of Canadian street youth, almost 30% of girls had dropped out of school before grade 8, meaning that they would potentially miss being vaccinated (NACI 2007).

Vaccine characteristics – evidence of potential benefit and harm

Gardasil® is effective in limiting pre-cancerous changes caused by HPV types 16 and 18, responsible for 70% of cervical cancers, and types 6 and 11, responsible for 90% of genital warts (Garland et al. 2007). The results from a recent systematic review (Rambout et al. 2007) show an overall Peto odds ratio of 0.14 (95% confidence interval 0.09–0.21) from combined per-protocol analyses for the reduction in high-grade cervical lesions caused by vaccine-type HPV strains compared to control groups.

So far the vaccine seems to be safe, with no increase in adverse events reported in the randomized trials done to date. As of the end of February 2009, PHAC had received 407 reports of adverse events following HPV immunization. The majority of these adverse events were not serious and are consistent with the results reported by clinical trials conducted prior to the approval of the vaccine, and can be expected with

the administration of any vaccine (PHAC 2009). In the United States, as of the end of 2008, there were 12,424 reports of adverse events following immunization (AEFIs). Seven hundred and seventy-two reports (6.2% of all reports) described serious AEFIs, including 32 reports of death. Disproportional reporting of syncope and venous thromboembolic events were noted with data mining methods (Slade et al. 2009). These findings must be interpreted against the limitations (possible underreporting) of a passive reporting system. Both CIC and NACI have accepted the vaccine as safe, and neither recommended a post-marketing surveillance campaign. In the absence of long-term data about the vaccine's safety, that acceptance seems premature.

Research questions and ability to evaluate

At the time of the decision to fund the vaccine, fewer than 1,200 girls under 16 had been studied (Merck now says this is 3,000), and then for an average of only three-and-a-half years. In the age group 9–15, the group being targeted in Canada, the vaccine is immunogenic in the short term but long-term efficacy has not been established (Gostin and DeAngelis 2007). The lack of efficacy data in this age group has also been noted by CIC (2007) and NACI (2007), but both agencies have assumed that immunogenicity will translate into clinical efficacy. Neither recommended any specific research program to validate this assumption. CIC did recommend linking a registry of HPV vaccine coverage with a registry of cervical cancer, as well as a national HPV sentinel surveillance system, but no action has been taken at the national level.

What will be the proper frequency for cervical screening for women vaccinated before adolescence? This question, which has not been answered, is important because the overwhelming majority of lesions with mildly abnormal cytology or histology are not related to either of the types that Gardasil® protects against. Raffle (2007), writing in the *BMJ*, points out that this finding means that screening in this cohort will yield a very high ratio of trivial findings relative to significant ones, where intervention has positive results. If HPV screening replaces Pap smears in vaccinated women, then this concern will be alleviated; but NACI did not deal with this issue, and CIC said only that there is a "need to define the role of HPV testing." Therefore, we cannot be sure what type of screening program will be available in the future.

A reduction in the HPV types 16 and 18 could lead to an epidemiological shift of HPV disease as one or more of the 15 other high-risk oncogenic strains moves to fill the ecological niche (Sawaya and Smith-McCune 2007). As with the other two questions posed above, there is no indication that this issue is being considered in any future research agenda.

Immunization strategy

The goals of any potential mass vaccination program need to be clearly articulated. CIC has stated that its goal is "to decrease the morbidity and mortality of cervical cancer, its precursors and other HPV-related cancers in women in Canada" through a combination of primary (vaccination) and secondary (screening) programs. If this is to be achieved through the eradication of HPV types 16 and 18 from the general population (the elimination of cancer caused by these types), then should boys also be vaccinated? However, Gardasil® is only now being tested in men, and the results of this trial are not yet available. If a reduction in the burden of harm from cervical cancer is the goal, then we need to know about the duration of immunity following a complete schedule of immunization. This question has not been resolved but has important implications. Lifelong immunity would result in a 61% reduction in the incidence of cervical squamous cell carcinoma, whereas 30-year immunity would reduce this to 6% (Van de Velde et al. 2007).

Feasibility and acceptability of the program

The success of a vaccination program aimed at school-aged girls will depend on the attitudes of clinicians and parents. Eighty-five per cent to 90% of Canadian family physicians, obstetricians/gynaecologists and paediatricians plan to recommend the vaccine (Duval et al. 2007), but only 70%–75% of parents of girls aged 8–18 indicated that they planned to get their children vaccinated (Ogilvie et al. 2007). The CIC's goal is to achieve a vaccination rate of 80% within two years of the commencement of the program and 90% after five years (CIC 2007). In practice, there has been significant variability in vaccination rates in school programs, ranging from 49% in Ontario to 87% in Quebec (Canadian Press 2009).

Cost-effectiveness

Is Gardasil® the most cost-effective measure for public health? The NACI strategy of immunizing every Canadian female aged 9–26 would involve vaccinating over 5 million females at a cost of $2 billion today for the vaccine alone. Table 1 summarizes the results of the three Canadian cost-effectiveness studies that have been undertaken so far (BC Cancer Agency 2006; Brisson et al. 2007; Marra n.d.). The cost per quality-adjusted life-year (QALY) varies substantially, depending on the underlying assumptions that go into the model; particularly important is how long immunity will last. Two of the models assume an uptake of at least 80% (BC Cancer Agency 2006; Marra n.d.), a rate that has not been universally achieved in Canadian provinces to

date. Furthermore, the study from the British Columbia Cancer Agency (2006), using a vaccine cost of $300 and assuming the need for one booster at $100, concluded that over a 26-year period the cost of the vaccine greatly outweighs that of avoiding treatment of HPV-related disease in the province ($373.6 million versus $54 million).

TABLE 1. Results of Canadian cost-effectiveness studies

Study	BC Cancer Agency (2006)	Brisson et al. (2007)	Marra (n.d.)
Assumptions	• 12-year-old girls vaccinated • Protection against HPV 6/11/16/18 • 80% uptake • Efficacy 100% • Booster shot required at 10 years • Cost per course $300 + $100 (booster)	• 12-year-old girls vaccinated • Protection against HPV 6/11/16/18 • Efficacy 95% • Lifetime immunity/30 years/30 years with booster • Cost per course $400 + $167 (booster)	• Grade 6 & 9 girls vaccinated (grade 9 catch-up) • Protection against HPV 16/18 • Vaccine compliance grade 6: 85% & grade 9: 80% • Efficacy 100% • Lifetime immunity/10 years • Cost per dose $134.95 + $12.66 administration (total, 3 doses)
Cost per quality-adjusted life-year (QALY)	• $45,000–$60,000 (2002 US dollars)	• $20,512 (lifetime) • $64,584 (30 years) • $36,981 (30 years with booster) • (2005 Canadian dollars)	• $25,417 (lifetime) • $113,078 (10 years) • (Canadian dollars, year not stated)

Equity

A key question is the public health outcome of a vaccination program versus the investment of an equivalent amount of money in outreach programs, such as more vigorous promotion of Pap smears and condom use, targeted to high-risk groups. Consistent condom use can reduce the risk of cervical and vulvovaginal HPV infection (Winer et al. 2006). A meta-analysis has shown that 54% of patients with invasive cervical cancer had inadequate screening histories, and 41.5% had never been screened (Spence et al. 2007). These groups of women are extremely difficult, but not impossible, to reach. In the mid-1990s, Australia instituted a program involving funded positions for women's health educators, provider education and public campaigns designed to increase cervical screening rates among Indigenous women living in the Northern Territory (Binns and Condon 2006). The screening rate subsequently improved, although in most areas Indigenous participation remained lower than national levels. In one part of the Northern Territory, however, it was considerably higher. In a US study, the use of health advisers and a nurse practitioner to perform

the screening increased the rates of breast and cervical cancer screening in low-income women, especially those in greatest need (Margolis et al. 1998).

Political considerations

Before the federal and Ontario governments made favourable decisions about the vaccine, former advisers to both governments registered as lobbyists to work for Merck through the public relations firm Hill and Knowlton. Part of their brief was "Proposed policy decision to support a childhood immunization program for HPV and funding related thereto." The SOGC received a $1.5-million grant from Merck (Page 2007). These revelations could raise questions about the role that Merck and its lobbyists played in the entire process.

Conclusion

A summary of the arguments for and against current Canadian policy appears in Table 2.

TABLE 2. Summary of arguments for and against current Canadian policy

	Positives	Negatives
Numbers	• More than 25,000 people in trials, larger than for most vaccines • Immunogenicity high in younger ages	• Few females under 16 studied
Clinical effects	• Effective against strains causing both genital warts and cancer • Appears to be highly efficacious if administered before exposure to the virus • Adverse effects thus far are minimal	• Vaccine is immunogenic in the short term in the 9–15 age group but long-term efficacy not established • Doesn't cover 30% of oncological strains, unknown potential for oncological shift
Cost-effectiveness	• Savings in future? • Cost per QALY gained within acceptable range but dependent on assumptions made in model	• Uncertainties about benefits • Is the price of the vaccine excessive? • Study done for BC Cancer Agency analysis shows vaccination program is much more costly than treatment of HPV at current vaccine price • Will use of the vaccine reduce frequency of Pap smears? • Will there be a need for boosters? • Will high-risk populations be immunized?
Endorsement	• Canadian Immunization Committee, Canadian Paediatric Society, National Advisory Committee on Immunization, Public Health Agency of Canada, Society of Obstetricians and Gynaecologists of Canada • Many other countries have approved Gardasil®	• Questions about possible conflicts-of-interest in decisions made by government and Society of Obstetricians and Gynaecologists of Canada

Our analysis of the national decision to recommend and fund a vaccination program using Gardasil® raises significant questions about the basis for this program. Many of the questions that we have posed, such as the ability to reach marginalized groups with the vaccine, could either be answered, or strategies to deal with the unanswered questions could be developed, relatively quickly. We are not alone in identifying gaps in the knowledge base and the need for additional research. Indeed, many of the points that we make were also raised by NACI and CIC. These questions could potentially have been investigated during an ongoing vaccination program, but the fact that they were not incorporated into the funding announced by the government, or clearly articulated by PHAC, suggests to us that they may continue to be relatively ignored while the focus is still primarily on vaccination rates.

Some may believe that we are holding this vaccine to a higher standard than is typically applied to other new vaccines. In response, we note that this vaccine is different from others, such as the ones for meningitis that have been recently introduced. Diseases such as meningitis can be rapidly fatal, and a quick response to decrease their incidence is justifiable without long-term studies. In this case, we do not believe that there is the need to rush to make decisions. What is the crisis that precludes waiting for better policy to be developed? In asking this question, we do not mean to minimize the pain and suffering that women endure when they have abnormal Pap smears, anogenital warts and, even worse, cervical cancer. However, the fact is that over 90% of women clear HPV infections within two years, and while the vaccine will reduce the prevalence of HPV infections, herd immunity will require several generations (Canadian Agency for Drugs and Technologies in Health 2007). Just because we have a vaccine does not mean that we should rush to implement a program of universal immunization without thinking through the policy implications. Failure to adhere to a rigorous process for recommending a massive vaccination campaign may severely damage the public image of the healthcare system.

Just because we have a vaccine does not mean that we should rush to implement a program of universal immunization without thinking through the policy implications.

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