

Canadian Women's
Health Network



Le Réseau canadien pour
la santé des femmes

HPV, Vaccines, and Gender: Policy Considerations

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Executive Summary

Cancer prevention remains a high priority for women and men in Canada, and critical steps for cancer prevention are identifying and eliminating the causes of such diseases. The federal government's recently-announced \$300 million investment toward a program for vaccinating girls and women with the currently available human papillomavirus (HPV) vaccine, *Gardasil* (manufactured by Merck Frosst) framed by some as a way to prevent cervical cancer in Canada, has generally been welcomed by a wide range of commentators. The policy commitment to improve the health of women and girls is laudable and emerging research about the effectiveness of immunization in reducing HPV prevalence is promising.

However, although HPV infection is necessary for the development of cervical cancer, and while evidence suggests that *Gardasil* may prevent primary infection with HPV types 16 and 18 (currently thought to be a necessary cause of about 70 per cent of cervical cancer cases), we propose that these facts be assessed within a broad context, which at this moment contains many unknowns, before immunization policies are developed and implemented.

A careful review of the literature, including that which was submitted by the manufacturer with its application for approval of *Gardasil*, reveals a sufficient number of unanswered questions to lead us to conclude that a universal immunization program aimed at girls and women in Canada is, at this time, premature and could possibly have unintended negative consequences for individuals and for society as a whole. We suggest that rather than giving widespread administration of this vaccine a "green light," a more appropriate policy at this time would be a "yellow light" of caution. We recommend that the funding announced by the federal government be used to support the research needed to answer the many questions outlined below; to fund a public education campaign to quell the unfounded anxiety that has been instilled by marketers of the vaccine that HPV represents a "new" or "imminent" threat; and to ensure equal access to Pap testing, including timely follow-up and application of improvements in testing. Only when there is a solid evidence base and an appropriately-provisioned cervical screening program accessible to all can we determine the most appropriate holistic strategy – and the place of vaccination in it – to address cervical cancer and the transmission of HPV between and among Canadian girls, boys, women, and men. We have been given an exciting opportunity to establish effective guidelines and to create a model of how to approach future vaccines. We must take full advantage of it.

In this paper, we summarize some of the major questions and concerns that need to be addressed before there is a full-scale roll-out of an HPV vaccination program. These closely reflect issues raised in the analytical framework created by Erickson et al.ⁱ in the context of the development of the National Immunization Strategy (NIS), and support efforts to ensure a comprehensive and systematic evaluation of all relevant factors before decisions regarding the importance of a new immunization program are made. As well, they echo some of the research questions identified as important in the Final Report from the Canadian Human Papillomavirus Vaccine Research Priorities Workshop held in Quebec City in 2005.ⁱⁱ We

hope raising these questions now will contribute to the deliberations necessary to ensure a responsible and transparent evidence-based decision-making process.

Our major points, summarized here, are discussed in detail in the text that follows. They are also summarized in a Commentary appearing in the 28 August 2007 issue of the *Canadian Medical Association Journal (CMAJ)*, online as of 1 August 2007.

1. There is no epidemic of cervical cancer in Canada. According to Canadian Cancer Statistics 2006,ⁱⁱⁱ approximately 400 women were anticipated to die of this disease in 2006.
2. Invasive cervical cancer typically follows a slowly progressive course that can be halted at one of various stages. Consequently, deaths associated with cervical cancer, relatively rare in Canada, but always unfortunate and not distributed evenly among women, must be considered as a failure in the adequate support of both the primary care and reproductive health services that would guarantee healthy living conditions for all women as well as ensure all women get appropriate Pap testing and follow-up.
3. Most HPV infections are cleared spontaneously. Recent research using available molecular detection technologies suggests that clearance occurs within one year for about 70 per cent of those infected, and within two years for 90 per cent. Thus, HPV infection and cervical cancer must not be conflated: most women who are infected with even a “high-risk” strain of HPV will not develop cervical cancer.^{iv}
4. The nature of an immunization program is necessarily dependent upon the definition of clear and tangible goals. To date, such goals have not been made explicit with regard to a Canadian initiative. Is the aim of the vaccination program the eradication of high-risk HPV types from the population? Or is the aim to reduce the number of cervical cancer deaths? These different goals require different strategies.
5. Information about the efficacy of *Gardasil* appears promising, but remains uncertain. Recent reports seem to suggest that *Gardasil*'s efficacy may be significant only for grade 2 cervical intraepithelial neoplasia (potentially removable pre-cancerous lesions 40 per cent of which regress spontaneously and which may not even be recommended for treatment), while the data are “insufficient to support a conclusion of efficacy for grade 3 cervical intraepithelial neoplasia or adenocarcinoma in situ.”^v

Related to this are other unknowns about the vaccine's effectiveness in the “real world” including the possible need for booster shots, concerns about altering the natural history of viral infection, and the impact of vaccination programs on safer sex practices and Pap screening rates, all of which highlight the essential need for careful health services research for the development of appropriate vaccination policies.

6. Relatively few young girls (about 1200 aged 9 – 15 years) were enrolled in the clinical trials of *Gardasil*. Of these, a mere 100 were nine years of age, with the youngest being followed for only 18 months.^{vi} Yet, based on the assumption that they will not yet have been exposed to HPV viruses, girls in this age group represent the priority “target”

population for mass vaccination. Clearly, this is a very weak information base on which to construct a policy of mass vaccinations for all girls aged 9 to 13, as per the National Advisory Committee on Immunization's (NACI) recommendations.^{vii}

7. Rigorous collection and analysis of reports on adverse effects are needed for risk-benefit assessments that would allow for truly informed consent by individuals offered the vaccine. A list of adverse events is being compiled in the USA Food and Drug Administration (FDA) Vaccine Adverse Event Reporting System (VAERS)^{viii} database, but because these reports are both incomplete and hard to interpret, there remains a need for careful and unbiased analyses of harm.
8. Media and marketing claims about the impact of HPV prevalence are very misleading and the naming of *Gardasil* as the “cervical cancer vaccine,” implying the vaccine eliminates all cervical cancer, is incorrect. The marketing of *Gardasil*, which began in the United States even before it had been approved by the FDA, has made it difficult for there to be reflective discussions between parents and children, health care providers and their clients, as well as among the public and policy makers, about the nature and meaning of HPV and of vaccination.
9. There is a great need for cost/effectiveness analyses of proposed vaccination programs, since the “added value” of the vaccine is far from clear: girls and women, even if vaccinated, will still need to practice safe(r) sex and have access to existing reproductive and primary care programs – not only for Pap testing, but for other aspects of reproductive care as well. Such analyses are usually done prior to the initiation of a mass vaccination program to ensure that the most efficient and appropriate approaches are taken.

At Issue: HPV, cervical cancer and an HPV vaccine

Over 100 strains of HPV have already been identified, of which 35 are known to infect the genitals and reproductive organs. These 35 strains are classified as either “low-risk” or “high-risk” according to their oncogenic properties. Low-risk HPV strains, such as types 6 and 11 covered by the *Gardasil* vaccine, cause genital warts that are not linked to the development of cervical cancer (though recent vaccine advertisements have likely greatly confused the public, since they fail to distinguish between genital warts and cervical cancer).

At present, approximately 15 high-risk types of HPV have been identified, two of which (16 and 18) are included in the *Gardasil* vaccine. Recent surveillance data associate these two strains with approximately 70 per cent of cervical cancer cases.^{ix} The overall prevalence of HPV (any type) ranges from 10.8 per cent to 29.0 per cent^x depending on who in the population is surveyed – and how – with the specific prevalence of HPV vaccine types 16 and 18 “relatively low.”^{xi}

With a healthy immune system, most well-nourished, non-smoking women who become infected with HPV will clear the infection from their bodies, with or without treatment. In fact, the Public Health Agency of Canada has reported that over 80 per cent of HPV infections often acquired at an early age were cleared spontaneously within 18 months.^{xii} This underlines the importance of not conflating HPV infection and cervical cancer: most women who acquire even a “high-risk” strain(s) of HPV will not develop cervical cancer.^{xiii}

Although cervical cancer can be deadly, this is, fortunately, relatively uncommon in Canada. According to Canadian Cancer Statistics, approximately 400 women were expected to die of cervical cancer in 2006.^{xiv} Invasive cervical cancer typically follows a slowly progressive course that can be halted at one of various stages. The introduction of screening programs and the public funding of such programs has both decreased death rates from cervical cancer and significantly reduced health inequities among women.^{xv}

Cervical cancer “starts” with the detection of abnormalities (pre-cancerous changes called dysplasias) by routine Pap smears; rarely does a woman experience any obvious symptoms at this time, hence the importance of regular screening. If detected early, and the abnormal cells removed entirely, cervical cancer will not develop. In fact, an approach that includes “watchful waiting” with repeat testing and treatment of any underlying infection is recommended in the recent guidelines for cervical cancer screening from Ontario, with smoking cessation and the institution of safer sex practices important adjuncts to this care.^{xvi}

It takes about 10 years on average for an untreated cervical dysplasia to progress to invasive cervical cancer. A 1995 Canadian National Forum on Cervical Cancer Screening reported: “In a perfect world, there ought not to be any deaths due to cervical cancer.”^{xvii} Cervical cancer is highly preventable, and deaths from it avoidable, because it can be detected and treated at an early stage.^{xviii} Women who die of cervical cancer are often those who either don’t have access to appropriate primary care and appear later in the disease stage, or who are not given proper follow-up after an abnormal Pap result.^{xix}

Although errors (procedural or other) can occur throughout the Pap screening process, these appear more likely to occur within for-profit and poorly regulated health service systems. Nevertheless, there is always room for improvement in the Canadian system – and not all provinces approach screening in the same (or most effective) ways. The new Pap testing technologies, such as liquid-based cytology, and HPV screening if a Pap test shows atypical cells, are being explored as ways to enhance screening programs in this country. Since these are recent developments, they have not been broadly assessed in primary care. Thus, their potential contributions to cervical cancer prevention is not yet known but should be considered as part of any review of Canadian cervical cancer prevention and management programs.

A 2003 study entitled, “The Safety Net: A Cost-Effective Approach to Improving Breast and Cervical Cancer Screening,” found that “1 person in 12 was not screened in the preceding 5 years, but these accounted for nearly two-thirds of invasive cancers.”^{xx} Women who lack access to regular Pap screening are disproportionately women living in poverty, immigrant and refugee women, women living with disabilities, women who have experienced sexual trauma/abuse, Aboriginal women, and women living in remote areas. Women who have sex with women also tend to be under-screened because their health care providers incorrectly assume they do not need to be tested.^{xxi xxii} Barriers to access are varied and include the absence of female health care providers, time constraints, costs (direct and indirect) of getting services, childcare, language and literacy differences, lack of knowledge, cultural differences, safety concerns (history of childhood sexual abuse and/or history of abuse at the hands of healthcare professionals), and health care providers’ attitudes towards cervical cancer.^{xxiii}

In view of these access differentials, it is interesting that income-related disparities in rates of death from cervical cancer diminished markedly in urban Canada from 1971 to 1996 most likely as a result of the implementation of effective screening programs.^{xxiv} Clearly, as the “Safety Net” study concluded: aggressive outreach to the rarely screened is both necessary and effective in *equitably* promoting and improving health.^{xxv}

At a 2006 University of Manitoba Continuing Medical Education workshop on “Eradicating Cervical Cancer,” data were presented which showed that women who developed cervical cancer in Manitoba had the same opportunity to be screened as others, but were still less likely to be screened.^{xxvi} Emphasizing this care gap was the estimate that had this screening occurred, there would have been only 34, and not 51, cases of invasive cervical cancer in Manitoba in 1999.^{xxvii} This suggests the need for better understanding of the reasons for “missed opportunities” and of the roles of physician, patient, and system failures in these. A vaccine cannot fill a gap created when physicians do not regularly screen patients; those who are vaccinated will still need routine Pap testing.

Research gaps: do we have enough effectiveness and safety information to initiate a mass immunization program?

According to data Merck submitted in applying for approval of the vaccine, clinical trials of *Gardasil* involved over 20,000 female participants ages 16 to 26 followed for an average of three and a half years. However, among this group were fewer than 1,200 participants aged nine to 15, the very group for whom the vaccine has been recommended, since they have been

thought to be unlikely to have been exposed to any HPV virus.^{xxviii} Moreover, a Merck official has indicated that of these 1,200 girls, only 100 were nine years old, and younger girls were only followed for 18 months.^{xxix} This raises concerns about the evidence base for Health Canada's National Advisory Committee on Immunization's (NACI) recommendation that all girls in Canada aged nine to 13 be vaccinated. Even Diane M. Harper, a leading researcher in the development of the human papillomavirus vaccine, has said that giving the drug to 11-year-old girls "is a great big public health experiment."^{xxx}

The general assumption in vaccinating 11- or 12-year-old girls is that they will not yet be infected with HPV, since this is below the usual age of sexual onset. But this may not be the case; substantial numbers of young girls and children may actually show evidence of current or prior HPV infection. For example, there are reports of a high HPV prevalence among newborns based on tests of nasopharyngeal aspirates or oral swabs.^{xxxi} Pediatric diseases have also been linked to certain HPV strains: juvenile recurrent respiratory papillomatosis is associated with HPV types 6 and 11, with these usually present in children younger than 5 years,^{xxxii xxxiii} while cutaneous HPV infections have been reported to be prevalent in about 50 to 70 per cent of children aged 1 month to 4 years.^{xxxiv} Other studies have also suggested that anogenital warts in pre-adolescent children are increasing in frequency, with HPV types 6, 11, 1 and 2 being detected in these lesions, and 3 to 35 per cent of cases being associated with sexual abuse.^{xxxv xxxvi} Though it could be argued that many of these infections will most likely clear before pre-adolescence, reports that almost 25 per cent of adolescent females were infected with HPV suggest that infection may have begun in pre-adolescence.^{xxxvii} In any event, these data do warn against assuming too quickly the lack of exposure to HPV in even young girls in developing vaccination programs and policies.

Efficacy and Effectiveness: There are persisting unknowns about the reported efficacy of *Gardasil*. An editorial in the *New England Journal of Medicine* commenting on the FUTURE I and II randomized, placebo-controlled trials of the HPV vaccine calculated that in the larger, FUTURE II trials, where the majority (93 per cent) of participants were not "virgins," "rates of grade 2 or 3 cervical intraepithelial neoplasia (CIN) or adenocarcinoma in situ were 1.3 in vaccinated and 1.5 in unvaccinated women, an efficacy of 17%."^{xxxviii} The editorial highlights, too, how efficacy was significant only for grade 2 CIN; and not for grade 3 CIN or adenocarcinoma.^{xxxix}

Journalist John Carreyrou, quoting from FDA and Merck presentations, recently reported that "in clinical trials, 361 of 8,817 women who received at least one shot of *Gardasil* went on to develop precancerous lesions on their cervixes within three years of vaccination, just 14% fewer than in a placebo control group."^{xl} Reacting to these numbers, a Merck spokesperson is quoted by Carreyrou as saying "the 14% figure is misleading because more than a quarter of the women in the study were already infected with HPV before receiving the vaccine, blunting its effect. ..." Carreyrou notes that the company tends to draw attention preferentially to a restricted subset of 4,616 trial participants who were mostly free of HPV when they were vaccinated, since "only 52 of these women went on to develop precancerous lesions on their cervixes over the next three years, 46% fewer than among the placebo group" (emphasis added).

Even if the difference between vaccinated and unvaccinated individuals were 46 per cent, this refers to the frequency of potentially removable pre-cancerous lesions and not to the rates of cervical cancer. At this time and given current data, a vaccine's impact on the incidence of cervical cancer is unknown – and, for ethical reasons, probably can never specifically be known: no one will merely observe a woman who is found to have lesions that necessarily precede cancer. These distinctions are highly relevant because the prior infection status of girls (and women) who would receive the HPV vaccine in a mass program will be unknown, since pre-immunization testing is not done. Clearly, then, measuring the effectiveness of any vaccine requires a specific definition of the “outcome” assessed and calculation in “real world” terms.

Duration and Nature of Protection: Besides the dearth of information on the short-term effectiveness of the HPV vaccine for girls in the youngest age group, the duration of its protection is also unknown: the longest follow-up reported has been only 60 months, and only 241 individuals were studied.^{xli} Thus, questions arise about whether a booster will be needed, and if so, when. Based on experiences with other vaccines (e.g., chicken pox vaccine), some have suggested that a booster shot for the HPV vaccine will be required after approximately ten years,^{xlii} but this remains speculative.

Questions about the nature of the vaccine's protection have also arisen. In this regard, the example of chicken pox is perhaps informative in yet another way, one that offers a cautionary tale: only recently has it been shown that immunity against chicken pox may be much shorter than models predicted, and that the short-lived nature of immunity has actually altered the natural history of viral infection, with “children between the ages of 8 and 12 years who had been vaccinated at least 5 years previously...significantly more likely to have moderate or severe disease than were those who had been vaccinated less than 5 years previously.”^{xliii} Whether this process will be echoed in those vaccinated against HPV remains to be determined.

Another unknown is the infectivity of other high-risk HP viral strains in the absence of competition from types 16 and 18. It has been suggested that *Gardasil* may have wider protection than against these two strains alone, but there is growing concern about potentiating the oncogenicity of other strains. The latter raises the question of whether there will be an epidemiological shift of HPV disease to currently less frequent oncogenic types when the pool of HPV types 16 and 18 is reduced. A recent study in *The Journal of the American Medical Association* on the use of the heptavalent pneumococcal conjugate vaccine in Alaska Native children is cautionary: it indicates that “since 2004, the invasive pneumococcal disease rate caused by non-vaccine serotypes has increased 140% compared with the pre-vaccine period.”^{xliv}

These newly emerging insights into disease processes in vaccinated populations from experiences with chickenpox and pneumococcal pneumonia highlight the need for research to explore how *Gardasil*, or any other HPV vaccine, might alter the natural history of HPV infections – and whether other HPV strains might move in to occupy the vacated niche – before engaging in a massive vaccination program.^{xlv}

Goals of Immunization: If the goal of a mass vaccination program is to block circulation of the virus, then vaccinating boys and men, “vectors” of the virus, would seem to provide indirect health benefits for women (in cases of male to female transmission), and possibly offer protection for males from genital warts and rare anal and penile cancers. Similarly, if a program’s goal is pathogen eradication and its correlate of “herd-immunity,” then again the possible need to vaccinate boys and young men needs consideration. Yet data indicating the effectiveness of vaccinating males, as well as the safety of doing so, both in the short and long-term, are not available. There are methodological challenges to carrying out research to obtain this information, but the high possibility of off-label use reveals the urgency and importance of such studies.

By contrast, a goal of cervical cancer reduction would suggest the need for a vaccine directed against more than the two high-risk HPV types (16 and 18) in *Gardasil*. In this regard, it is worth noting that *Gardasil* is but the first of a variety of HPV vaccines under development, with another – *Cervarix*, GlaxoSmithKline (GSK) – recently approved for use in Australia and the European Union. Its coverage against oncogenic HPV strains is said to be different from that of *Gardasil*^{xlvi} and any efforts to reduce cervical cancer would seem to require a direct comparison of products before any one vaccine is adopted as policy. In Canada, this may be of special interest if, as is claimed^{xlvi}, *Cervarix* protects against strains 31 and 45 (in addition to 16 and 18) given that 31 may be predominant in Nunavut.^{xlvi}

A recent editorial in *Nature Biotechnology* suggests that in all the extensive marketing for *Gardasil*, a clinical case for the vaccine was never fully made.^{xlvi} In fact, the data from the clinical trials, while positive, are not robust – certainly not sufficiently so for a product that is to be administered to healthy people for prevention where the bar must always be even higher than it is for a medicine to be used to treat a serious illness.^{li}

When acellular pertussis vaccines were introduced in Canada, “safety above all other considerations was decisive for their immediate adoption.”^{lii} Other pertinent features requiring attention in the immunization decision-making framework, features *not yet addressed with regard to any HPV vaccine*, include the administration schedule, the nature and characteristics of any immune response, immunogenicity in different population groups, effect of the vaccine on the transmission of the specific and related organisms, rates and severity of adverse events, contraindications, precautions, and potential interaction with other vaccines.^{liii} Most importantly, whatever the list of features needing clarification, we need to keep in mind the overarching issue: “Have important research questions affecting implementation of the program been adequately addressed?”^{liiv} With regard to *Gardasil*, the answer to THIS question is “no.”

In fact, almost all the published material we have about *Gardasil* comes from researchers supported directly or indirectly by the pharmaceutical company that developed the vaccine, a company that has been heavily advertising the vaccine throughout the American media. This underscores the urgent need for further research by independent investigators – besides emphasizing the requirement for explicit and detailed disclosure of potential conflict-of-interest information by all the investigators as well as by all who are making regulatory and policy decisions about this vaccine (*Gardasil*) and all others to come, including the posting of

full data submitted for regulatory approval, something beyond that which is required by a trial registration process.^{lv}

HPV vaccination in the “real worlds” of girls and women: is it the best strategy?

Just as there is insufficient research on the safety, effectiveness, and duration of protection of the HPV vaccine, there are also gaps in our understanding of the potential impacts of the vaccine upon health care behaviors in the “real world.” Without these data, population-based vaccination programs cannot be evidence-based.

The link between some strains of HPV and cervical cancer, the differences between types of HPV, and the natural course of HPV infection are issues poorly understood by many in the general public. It is critical that public health agencies undertake a broad-based public education program about HPV and its role in cervical cancer. This would enable those who are offered a vaccination to make a truly informed decision about its use.

The advertising campaign introduced by Merck is simplistic at best. It leaves the impression that the vaccine prevents “all” cervical cancer although the “small print” seeks to clarify this. Existing education programs already need to be enhanced to promote use of Pap testing; these programs would need serious updating to supply accurate information and to correct the possible misunderstandings created by marketing HPV immunizations. As the editorial in *Nature Biotechnology* suggests, if Merck was running a public education campaign it would have included “greater awareness of disease risk, safe sex, condom use” and improved Pap screening programs.^{lvi}

There is an overwhelming consensus that even if vaccinated, girls and women will remain at risk for the development of cervical cancer if they become infected by other high-risk strains of HPV not included in *Gardasil* or any other vaccine. Therefore, all girls and women who are immunized will still have to continue to practice safe(r) sex and have regular Pap smears. At the present time, however, we lack the necessary information to know how girls and women will respond to messages for Pap testing or indeed seek other reproductive health care if, despite the “small print” in patient handouts, they believe *Gardasil* to be a “simple fix” that means they are “vaccinated against cervical cancer.” Will the health practices of teens and women change in any way?

It would surely be paradoxical if a false sense of security were to lead to an “iatrogenic” increase in cervical cancer rates because girls and women stop having regular Pap screening. Similarly, there are concerns that a false sense of security could lead vaccinated individuals to be less vigilant in using safe(r) sex practices, resulting in an increase in STIs such as chlamydia and even human immunodeficiency virus (HIV) infections.

The extent to which vaccination alters potentially riskier behaviour is currently unknown, yet this information is essential for developing an evidence-based policy approach. The absence of implementation studies or other research that addresses these concerns in the Canadian context does not mean that these concerns should be ignored. To the contrary, they have been ranked among the most important when experts at the 2005 Canadian Human Papillomavirus Vaccine Research Priorities Workshop were asked to identify where research was needed.^{lvii}

Also not to be ignored with regard to implementation is the actual vaccine regimen. The current protocol for *Gardasil* involves three shots over a period of six months. This raises questions about how to ensure that everyone receives all three shots. And if only one or two instead of three shots are obtained, will there be any change in the effectiveness of the vaccine or its duration?

Uncertainty about if, when, and how frequently boosters will be required raises another challenge for care, and those who pay for that care, in the “real world.” As uncomplicated as it may be to reach nine-year-old girls in school (on the assumption that the issue of “opt-in” versus “opt-out” consent is resolved), reaching a woman 19 years of age or older for a follow-up booster program may prove to be more difficult; it is very likely that the same challenges involving access now apparent in Pap screening programs will be reproduced, with marginalized populations, such as homeless youth who may be at higher risk of acquiring the virus, unable to be reached for a booster shot at the age (20 to 24 years) that shows the highest HPV infection rate. This highlights the need for a national registry to manage the reminder program. With this in mind, one cannot help but ask why there has not been a national Pap registry established similar to the registries in British Columbia and Europe. Or why the establishment of a national Pap registry is not seen as a pre-requisite to any possible vaccination program.

The costs: added value, lost opportunity costs and impacts on health care services

Gardasil is the most expensive childhood vaccine proposed for mass use; it currently costs \$404 for the three required doses. Uncertainty about when and how frequently a booster shot may be required combined with insufficient knowledge of the extent to which the vaccine provides better or longer-lasting immunization than does natural immunity following exposure, create serious challenges in generating economic costing models. A background paper written by economist and epidemiologist Hans Kreuger for the BC Cancer Agency found that introducing *Gardasil* in British Columbia in 2005 (assuming a cost of \$330 for the vaccine and a booster at \$100) would save \$54 million in treatment costs over 26 years but at a cost of around \$373.6 million.^{lviii} Kreuger concluded that to break-even, the cost of the vaccine would have to be \$45 and the booster, \$15. In a recent article in the *Canadian Medical Association Journal*, Pauline Comeau estimated that the cost of vaccinating 5 million females (per the NACI’s recommendations) would be \$2 billion for the vaccine alone; with this being a recurring cost.^{lix} This does not include costs of doctors, nurses, or support staff time, equipment, information systems and educational materials, without mentioning the cost of a booster program. No one argues with the fact that there will be a “huge initial outlay” with no lives saved for the first 20 years of the program.^{lx} But, to determine if this is a wise outlay, we need proper costing estimates over the long term.

Given that HPV vaccination must not and cannot lead to changes in personal safe(r) sex practices and access to primary care that includes Pap testing, it becomes essential to know if a vaccination program can be justified on the grounds of being cost-effective. For example, there is, as noted earlier, the potential for the vaccine to lead to an increase in costs for the treatment of sexually transmitted infections if any false sense of security results in changed behaviours and a decrease in regular Pap screening and follow-up. This possibility, along with

untested assumptions about decreased costs from possible reductions in colposcopies performed, repeat Pap tests and client stress, all need to be explored in sensitivity analyses of estimated costs.

Other missing evidence related to the economic costs of a vaccination program includes the extent and nature of adverse reactions to the vaccine. Not only are adverse reactions a potential harm in themselves, they could lead to additional health care costs if treatment or other remedies are required. And since governments are responsible for providing such care, the extent of these costs requires some estimation.

Moreover, there are also “lost opportunity” costs to consider before implementing an HPV vaccination program – and these may be significant. The \$300 million the federal government is planning to provide as start-up funding would only cover 750,000 of the 5 million females the NACI has recommended be vaccinated. Nor is this amount anywhere near what the costs will be for the next few decades. Will the provinces, already calling for increased healthcare funding, be able to fill the gap? And what will happen to resources needed for existing reproductive health services? An improvement in Pap screening will still need to occur and it could be argued that enhancing Pap screening programs has other added value since these improvements will mean women having increased connection with primary care services, allowing for other reproductive health and health promotion activities to occur. An analysis of the National Cervical Cancer Screening Program in Australia done by the Centre for Health Economics Research and Evaluation points to the necessity of such evaluations^{lxi} as did the Priorities Workshop participants when they met in Québec City,^{lxii} stressing how both feasibility and cost-effectiveness are main evaluative categories in an immunization decision-making framework.

Evidence-based planning and policies

The advertising campaign for *Gardasil* has engendered fears and propagated false promises. For media to be calling *Gardasil* the “cervical cancer vaccine” is misleading. With the longest follow-up being five years and a latency period of at least 10 years, “eliminating cancer,” even just those cases associated with HPV strains 16 and 18, can only be seen as hypothetical. Yet we are given the impression by advertisements and media of a public health emergency: to wit, a notion that a noxious infection exists, and that governments and loving parents, particularly mothers, need urgently to take action to protect their daughters.

The public, as well as policy makers, must be provided with sound scientific (molecular, epidemiological, and immunological) and social evidence for vaccination as well as the potential benefits and harms expected from widespread immunization with the HPV vaccine and this information must come before governments allocate huge sums of already limited health care dollars to such programs. It is time to take a breath and reflect on what we know, what we don't know, and develop a plan based on solid, reliable evidence that adds value for everyone.

To be clear, if and when evidence shows that an HPV vaccination program can be successfully implemented to meet pre-determined goals in Canada, it must be publicly-funded and fully accessible. Lack of financial resources must not preclude any girl or woman from

receiving what has been sanctioned by health officials. However, concern about how public funds are used to promote and protect the health of girls and women dictates our giving consideration to broader issues, including the needs of the marginalized and most vulnerable groups in society. Government support for HPV vaccinations must not perpetuate existing health inequities. Instead, such programs ought to reduce health inequities through thoughtful, comprehensive, evidence-based approaches that permit those most at risk to benefit.

The impact of ongoing problems with the regulatory process

The approval of *Gardasil* and the manufacturer's expensive and extensive marketing campaign aimed at consumers, providers, and policy makers in North America and Europe, has made it difficult for a reflective evidence-based discussion to occur between parents and children, between health care providers and their clients, and between the public and policy makers.

The need for – and a government commitment to – a more transparent process for drug and device approval within Health Canada, one that also includes sex- and gender-based analyses and takes into account the broader context within which these products are evaluated and used, has been a long-term demand by women's health advocates.^{lxiii} The introduction of public consultations in 2006 on breast implants (as well as on *Vioxx*), initially gave hope that a new and more transparent approach was underway. Putting aside their problematic nature, it is disappointing that there has been no public consultation at all on the approval of the HPV vaccine. Moreover, the criteria by which the product was evaluated, or the degree to which the gendered and equity aspects of the vaccine were assessed as part of the decision-making process, have not been disclosed.

At the same time, there is evidence of other forms of active lobbying to obtain support for *Gardasil*. For example, in the United States, early legislation requiring mandatory vaccination for young girls (in Texas) has been linked to targeted lobbying efforts by Merck. It has also been revealed that Women in Government, a national association of state legislators particularly in support of HPV vaccines, received funding from Merck. Canada has not been immune from such efforts, either. Thus, we've learned that a lobbyist with past ties to Prime Minister Stephen Harper, has been retained by the pharmaceutical company, Merck Frosst.^{lxiv} Merck Frosst stands to benefit from federal funding for a vaccination program said to prevent cervical cancer,^{lxv} particularly when the Finance Minister states that the \$300 million allocated in the budget for this is “targeted for *this* (emphasis added) HPV vaccine; they are not to be used for other purposes.”^{lxvi}

The relationship between lobbying and marketing for health-related drugs and devices and increasing health care costs, as well as increased risks for patients has been demonstrated repeatedly^{lxvii} leading to calls to limit “direct-to-consumer advertising” of pharmaceuticals and to regulate advertising and drug detailing to professionals.^{lxviii} The constant overstepping of boundaries in the marketing of *Gardasil*, added to the fact that most of the research about it has been supported by its manufacturer, suggest caution in accepting claims about the vaccine, emphasize why limits on marketing are needed, and raise concerns about why this vaccine was given unexpected federal support in the spring budget. Is *Gardasil* an early

example of a vaccine that fits within the new paradigm of “disease promotion” to sell products?^{lxix}

Conclusion and Recommendations

We unhesitatingly appreciate government interest in women’s health. However, to promote and protect women’s health most effectively, and to work towards the prevention of deaths from cervical cancer in Canada, we should not focus only on a universal HPV vaccination program at this time when there is an urgent need for prompt and clear answers to the many questions outlined above, with these answers coming from scientific research and not public relations campaigns.

Gardasil represents the first of what will likely be many vaccines targeting high-risk strains of HPV and how we proceed now will set the precedent for others, such as the GSK product, *Cervarix*. The foundation of a successful vaccine program must be solid evidence-based research and we presently have the exciting opportunity to complete this work and develop a model for current and future HPV vaccination programs with clearly defined and measurable health outcomes. Importantly in developing these programs, we must be certain that vaccinating a population of girls and women in Canada who are already mostly well protected by their own immune systems, safe sex practices, and existing screening programs at an estimated cost of over \$2 billion will not perpetuate the existing gaps in care and leave the actual death rate from cervical cancer unchanged. In developing a model HPV program, the following are some short-term priorities for action:

1. Governments should begin immediately to educate the public about the reality of cervical cancer, HPV infections, and vaccinations to quell anxieties about cervical cancer and HPV, and to emphasize the importance of healthy personal practices including use of barrier methods, good nutrition, smoking cessation, regular Pap smears and screening for sexually transmitted infections.
2. Federal, provincial and territorial policies for reproductive health care should be reviewed, including an assessment of the place of any vaccination program within existing services for the prevention and management of cervical cancer.
3. The goals of any potential mass vaccination program need to be defined. If cervical cancer reduction is the goal, then the possibility of favouring safe and effective vaccines that cover a broad range of high-risk viral strains should be considered. If the goal is to eliminate HPV infections, then data on how to approach boys and men, as well as girls and women, and how to manage newly identified oncogenic HPV types within an immunization program, are essential.
4. Head-to-head comparisons of different vaccines carried out in government-supported research programs, free from any conflict-of-interest need to be undertaken to collect the data needed for evidence-based policy and healthcare decision-making.
5. While further research is underway, additional investments in improving reproductive health programs for girls, boys, men, and women should be made. This includes providing further funding for:

- Population-based outreach Pap-screening services. Efforts to ensure that appropriate screening occurs will be required to reduce the numbers both over- and under-screened, with particular attention to Aboriginal, racialized, immigrant, homeless, and other marginalized girls and women.
- Employing female community-based health care workers to provide screening.
- Exploring the training of women to do self-sampling for Pap and/or HPV tests.^{lxx}
- Access to free and low-cost male and female condoms.
- Engaging public health nurses in following up with women with atypical Pap results.
- Screening programs augmented with newer technologies such as use of liquid-based Pap testing and HPV genotype testing in women who have abnormal Pap test results.
- Initiating a broad, national HPV prevalence and typing study.
- Establishing a national Pap test registry that incorporates a follow-up component.

An investment in improving the Pap testing process for all women in Canada would be both efficient and economical. An added value of this investment is improved monitoring for and treatment of other STIs. Furthermore, it would offer an opportunity for delivering additional reproductive health promotion and disease prevention services including nutrition, smoking cessation counseling and preconception planning. Moreover, the creation of a registry would be useful to resolve challenges – such as managing reminders – in Pap screening programs, which too often do not reach marginalized populations such as homeless youth, who may be at higher risk of acquiring the HPV virus.

6. Strengthen the regulatory framework for the approval and monitoring of drugs, vaccines, and devices by including sex, gender, and diversity analyses; requiring robust safety and effectiveness reviews prior to approval; prohibiting direct-to-consumer advertising; and regulating the marketing of drugs, vaccines, and devices to providers. Similarly, consideration needs to be given to managing how governments respond to “disease promotion” campaigns initiated by advocacy groups and industry, particularly when these campaigns conflict with already established national public health goals.

In summary, the public, as well as policy makers, must be provided with sound and comprehensive multidisciplinary evidence for vaccination as well as unbiased data about the potential benefits and harms expected from widespread immunization with the HPV vaccine, and all this information must come **before** governments allocate huge sums of already limited health care dollars to such programs. Individual girls and women, as well as policy makers, can only make truly informed decisions about vaccinations when they have all the evidence.

At this point in time, there are more questions than answers.

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