



The Society of Gynecologic Oncologists of Canada

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GOC Responds To Public Concerns Regarding HPV Vaccine And Cervical Cancer Prevention

In Ontario, as of September 2007, the HPV vaccine will be freely offered through the school system, for the next three years, to girls entering into grade eight. Distribution of the HPV vaccine will be through a voluntary immunization program that will leave parents and their children with the decision of whether to vaccinate or not. The recent media blitz surrounding the HPV vaccine, although welcomed for the attention given to the often-neglected issue of cervical cancer, has been profoundly negative. In fact, the rhetoric by its very tone has the potential to derail a major advance in public health and cervical cancer prevention. It is imperative that a fair and balanced view of the HPV vaccine be presented so that parents and children can make informed decisions.

The burden of cervical cancer, and its precursors, has often been misrepresented as affecting only 1,400 women yearly, from which 400 will die. Some critics have suggested that there is no epidemic of cervical cancer in Canada that requires a move to HPV vaccination at this time. They contend that the problem is effectively dealt with by routine cervical screening with the Pap test, and this strategy is sufficient to keep the disease at bay. They would argue that the HPV vaccine should not be introduced, as proposed, until more research regarding dosing schedules and long term effects are fully understood – essentially maintaining the status quo for the time being. However, one must look a little deeper at the true burden of the disease to realize that the current prevention strategies are limited in the light of new technologies.

Prevention of cervical cancer comes at a very high price, in both human and financial terms. The current approach, a secondary prevention strategy (i.e. identifying a disease, or its precursors, and treating it while it is still curable) is based on Pap test screening. When a Pap test is abnormal, as is the case for approximately 400,000 Canadian women each year, cervical abnormalities are identified and results must be followed-up. This requires further Pap testing, additional visits to the doctor, and in many cases treatment to eradicate the cellular abnormalities. While treatment is typically localized to the cervix, and is successful at eradicating pre-cancerous

abnormalities, it is not without problems. For some, treatment has resulted in infertility, for others pain, infection or bleeding - sometimes an urgent middle of the night visit to the local hospital emergency is required. Treatment for pre-cancerous abnormalities of the cervix results in anxiety, inconvenience, and intrusion, all of which may have a significant overall negative psychological impact.

While this secondary prevention strategy has been successful in reducing cervical cancer incidence since the early 60's, there has been minimal or no reduction of cervical cancer in the last 15 years. Up to 25% of Canadian women are seldom or never screened and these include women from the most vulnerable populations – this is an issue of equity and access.

Our current approach of testing over and over in the hope of picking up early abnormalities is based on a redundancy paradigm that was fuelled originally by a lack of understanding of the cause of cervical cancer. It works only at great cost, estimated at approximately 300 million dollars per year, and the need for an infrastructure within the health system to screen virtually every woman. In Canada, we have not been able to mount the political will to take this process to the next step where it will become more effective.

Over the past 30 years, three major Canadian reports have recommended organized cervical screening information systems at the provincial/territorial and/or national levels. Such a system would keep track of individual Pap test results, the need for repeat tests or updated tests, and would ensure that each eligible woman and their doctor would be sent reminders about when to have a Pap test. The need to move from a spontaneous system, where a patient gets a Pap test only if they turn up to receive one, to that of an organized electronic system, was advocated in each of the three national reports. Despite the overwhelming amount of evidence of the benefits of organized screening approaches, and repeated advocacy efforts, cervical cancer prevention using a secondary approach has been stalled for many years. Yes, overall rates have been reduced over time with the Pap test, but unless change occurs, cervical cancer rates will go no lower.

It is now known that the cause of cervical cancer is an oncogenic cancer-causing HPV viral infection that is transmitted sexually. For the first time it is possible to employ a primary prevention strategy through the HPV vaccine. The HPV vaccine acts to stimulate the immune system to prevent the infection responsible for cervical cancers, and related pre-cancerous lesions, before they can develop. Thus, there is the need to implement this new strategy, based upon a biological paradigm, whereby the majority of the disease is prevented before it can occur. Not only does primary prevention have the potential to increase the standard screening interval from once every two to three years, to perhaps once every five years, but more importantly, the vaccine has the potential to greatly reduce the number of abnormal Pap tests, with the associated follow-up and treatment implications.

There can be no argument, even from the opponents of HPV vaccination, that the tenets of primary prevention are vastly superior to that of secondary prevention.

The implications of this biological paradigm argue strongly not only for vaccination programs to reduce the burden of the disease, but also for a fundamental shift in monitoring and testing for specific viruses. Secondary prevention strategies will still be needed under this new paradigm; however it is hoped that this will occur through linkages with existing cervical cancer screening programs and networks, and over time their focus will be revised.

The efficacy data around the HPV vaccine are sound and compelling. A systematic review of randomized trials (reported in the August 2007 issue of the CMAJ) clearly shows almost 100% protection from HPV infection and related disease caused by four major HPV subtypes (6,11,16,18). These subtypes account for 70% of all cervical cancers and 90% of all genital warts. The vaccine has been shown to be effective over five years of follow-up.

The argument that cervical cancer was not an endpoint in these studies, and as such cannot justify the implementation for cervical cancer prevention, is not valid. Endpoints in the trials were carefully chosen with the input from regulatory agencies including the U.S. Federal Drug Administration (FDA). These endpoints were surrogates for cancer (i.e. high grade precancerous lesions and infections with high grade risk types) simply because the long duration of the natural history of cervical cancer (decades) would make the endpoints of cervical cancer unmanageable and unethical in these studies.

The argument that investigation on about 1,200 girls aged 9 to 15 years of age cannot justify the use of the vaccine in the recommended 9-13 age cohort does not tell the whole story. All of the trials to date report data on outcomes of disease or infection for thousands of women between the ages of 15 and 26 years of age. With FDA approval, the younger age group was chosen only for immunogenicity data (i.e. to look to see whether this group would make antibodies against the HPV subtypes to a level equal to or greater than the 15 to 26 year age group) and not on efficacy (which addresses protection against infection). This is not only understandable but is practical as well. It would be unethical to submit younger girls to biopsies and examinations, especially when this age group generally does not have exposure to HPV infection. In the immunogenicity studies, the antibody responses were much higher than in the older age group. These data predict well for persistence of protection over time, and also provides the rationale for inoculation at an earlier age. Also, the vaccine was most effective when given prior to exposure to HPV infection.

In addition to the efficacy data established in the randomized trials, large ongoing phase IV trials (some groups being followed for life) are being conducted. These groups are five or more years ahead of any population implementation that we would choose to do now in Canada. The data from these groups will be shared worldwide to further inform issues regarding HPV vaccine implementation.

The issue of whether a booster will be necessary is important, and while there is presently growing evidence of long-term immunity, that data will need to be monitored prospectively. The situation is not unlike the precedent of the hepatitis B vaccine that is now routinely administered in schools, and one that uses the same vaccine technology with similar long-term protective effects. In addition, there are also ongoing reports from the various trials of immune memory responses in which women that are challenged with the HPV antibodies after 5 years are showing that they are able to mount a response.

The randomized trials, which were very tightly monitored for safety events, showed that there were more minor adverse events such as pain, redness, or swelling at the injection site associated with the vaccine. However, there were no differences in the number of serious adverse events or in deaths between those who received the HPV vaccine and those who received an inert placebo injection. These compelling data show that severe adverse events, even death, can occur in a study population, or in the real world, even when there are no reasons for such reactions (such as a placebo injection). The HPV vaccine has also been subjected to ongoing rigorous review by regulatory bodies around the world including Health Canada and the U.S. FDA. There is consensus by experts about the safety of the vaccine. With over seven million doses of the vaccine distributed in the USA alone, rates of serious adverse events have been less than expected, at approximately five percent of the 2,531 adverse events reported to date (U.S. VAERS database). This is lower than the average 10%-15% event rate seen with other similar vaccines. To date there has been a lack of causality related to the vaccine for the serious adverse events that have occurred. Based on this data, the American Advisory Committee on Immunization Practices has recently confirmed their support for the safety of the vaccine.

There are other issues that must also be addressed. One is that the HPV types not covered by the vaccine may take the place of the viruses that we are protecting against. This is considered by most experts to be a theoretical concern only, but to be safe, ongoing surveillance will be necessary.

It has also been speculated that girls may be more sexually promiscuous because they have had a vaccine to prevent against some types of HPV. This is wild speculation at best; it may very well be that greater awareness of sexually transmitted infections may have the exact reverse effect.

Other concerns focus on how to ensure equitable access to the vaccine, especially in under-serviced areas or on the impact to the screening system. Will women forget to get screened, or will the lack of a cervical screening registry become more of an issue? How do we tell who has been vaccinated and who has not? How do we make sure that girls and women will get the actual three doses and not just one dose? Are two doses as good as three doses? What about the cost? Is it cost effective? Is it the best way to spend our health care dollars to protect the health of women against this disease? Do we have the educational tools required to provide women, girls and parents with enough information to make an informed decision in a voluntary vaccination process? All these questions can be addressed through the ongoing integrated monitoring of vaccine implementation programs.

Therefore, what is the impact of waiting 10 to 20 years to see the results of cervical cancer rates drop before implementing the vaccine? What is the impact of a generation of adolescents not protected against the virus while we have the technology available to us? That needs to be figured into the equation. These questions all fall into the realm of implementation science, the next part of the story. Critics are correct; the data of how to do this right and for the best cost-effectiveness are not complete. This issue has received tremendous focus by experts across Canada leading to many documents outlining the strategies required for appropriate data gathering and infrastructure required to answer some of these questions.

As far as the cost-benefits are concerned, several modeling studies have quantified the possible impact of vaccination. Most of these studies show cost-effectiveness in favour of vaccine implementation versus other traditional strategies. The recent August 2007 CMAJ article by Brisson et al. reports that the number needed to vaccinate to prevent a cancer death with the HPV vaccine is actually superior to similar numbers than for the influenza, the meningococcal and the varicella vaccines.

A rush for needles into arms however is not the simple answer. Implementation must be done in concert with enhancing existing cervical screening programs, including the ideal of a cervical cancer-screening information system, advocated for over 30 years, and a parallel integrated strategy for the systematic monitoring of vaccine uptake and immunization outcomes. An information system would not only monitor adverse events and ongoing efficacy issues, but also provide information on implementation datasets needed to advance our knowledge (long term efficacy, optimum dosing, the need for boosters, impact on the health system, etc). To date the rhetoric has focused on other issues but in reality a key missing piece to the puzzle is to advocate for an organized implementation infrastructure. This part of the process will need to have the highest profile as the biological approach to this disease eradication unfolds. Will we have to wait another 30 years for the infrastructure pieces to fall into place to complete this puzzle? This is the drum-beat that should be used by all stakeholders, from

across the many different perspectives, to advance the state of the art in this very important women's health issue.

The controversy in the lay and medical press belie the multitude of perspectives on this issue – socially charged as it crosses sexual issues, religious issues, women/girl's issues, health-related politics, federal and provincial politics, big pharmacy, and not least money. While it is easy to see how viewing these incomplete datasets around implementation as a lightning rod for opposing perspectives, one must not lose sight of the big picture. The burden of disease, the stalled nature of cervical cancer prevention, and the impact of primary prevention have created not a perfect storm, but a perfect opportunity to galvanize the various stakeholders. What is now needed is to put our shoulders behind the eradication of cervical cancer not as a possibility but as a reality. With the HPV vaccine, the ongoing monitoring, follow-up, and integration with existing cervical cancer prevention practices will provide a lasting framework for success in the reduction of the burden of cervical cancer.

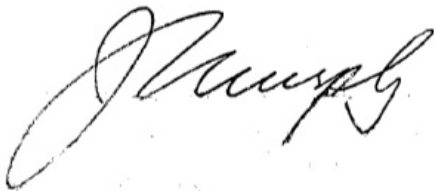
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