**HPV Vaccination Programs in Canada**

**ARE WE HITTING THE MARK?**

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**Introduction**

In 2007 the federal government allocated $300 million over three years to the provinces and territories on a per capita basis to support the launch of a national vaccination program against human papillomavirus (HPV), the putative cause of cervical cancer. All of the provinces as well as the Yukon Territory responded by introducing vaccination programs targeting various cohorts of females between the ages of 9 and 17.

This article i) compares how each province and territory has designed their HPV vaccination program in response to this federal allocation, ii) reviews cost implications, with preliminary comments on cost effectiveness, and iii) explores possible future applications of HPV vaccines in preventing other HPV-related diseases.

**Background**

In July 2006, Health Canada approved a quadrivalent vaccine that protects against infection with two high-risk types of HPV (16 and 18) and two low-risk types (6 and 11). A second vaccine that protects against HPV 16 and 18 has been submitted to Health Canada and is awaiting approval, and therefore is not included in this article. HPV types 16 and 18 cause approximately 70 per cent of cervical cancers, while HPV types 6 and 11 cause approximately 90 per cent of ano-genital warts. The quadrivalent vaccine is very effective in preventing HPV infection and the associated pre-invasive changes in the cells of the cervix.\(^1\) It is assumed that, as a result, invasive cancer of the cervix will also be prevented.

The development of the vaccine to help prevent cervical cancer demonstrates how basic research can make a difference. Dr. Harald zur Hausen was recently awarded the 2008 Nobel Prize in Medicine for finding there are multiple HPV genotypes, for molecularly cloning HPV 16 and 18, and for demonstrating that HPV DNA is present in a majority of cervical cancers. He was able to implicate HPV 16 and 18 as the principal viral oncogenes and suggested their continued expression con-

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**TABLE 1** Recommendations by the National Advisory Committee on Immunization (abridged)*

| Females 9-13 | Recommended – before the onset of sexual intercourse, efficacy would be the greatest. |
| Females 14-26 | Recommended—even if they are already sexually active, may not yet have been infected and very unlikely to have been infected with all four HPV types. |
| Females 14-26 who have had HPV infection, cervical cancer, or genital warts. | Recommended—these women are unlikely to have been infected with all four HPV types. |
| Females > 26 | No recommendation at this time. Studies are ongoing. Can be considered on an individual basis. |
| Females < 9 | Not recommended. |

**Males**

Not recommended at this time. Immunogenicity data are available but the efficacy of this vaccine is as yet unknown.

**Immunocompromised persons**

Can be administered to persons who are immunosuppressed as a result of disease or medications; however, the immunogenicity and efficacy in this population are not known. Immune response to the vaccine might be less than that in persons who are immunocompetent.

**Pregnancy**

Not recommended. Data limited. If a woman is found to be pregnant after initiating the vaccination series, completion of three-dose regimen should be delayed until after pregnancy.
tributed to the tumorigenic phenotype. Earlier this year, he was also awarded the Canadian Gairdner Award in recognition of his work.

Current Recommendations for the Vaccine

The vaccine is given as three separate 0.5 mL doses, using a zero, two and six month schedule. The minimum interval between the first and second dose is one month.¹

Provincial Vaccination Programs

Table 2 summarizes the provincial vaccination programs. It includes the year the program started, the ongoing female cohort immunized, and the short-term catch-up of female cohorts (if any). In all provinces and one territory, the HPV vaccination program offers free HPV vaccine to all females in at least one of grades 4 to 9 through school-based clinics administered by local public health units.

Newfoundland and Labrador, Prince Edward Island, Nova Scotia and Ontario implemented an HPV vaccination program in September 2007, each targeting one age group of pre-adolescent females. In 2008, Newfoundland and Labrador increased their program to include a second cohort in grade 9. The remaining six provinces and the Yukon Territory commenced their programs in the 2008-09 school year.

As can be seen in the table, the dissemination of the vaccine by age and grade varies widely across the provinces. Quebec, with the most comprehensive program, started vaccinating girls in grades 4 and 9 as of September 2008. Girls up to the age of 18 can also be vaccinated upon request. If the girl is under 14, her parents will have to sign a consent form.

Prince Edward Island, Nova Scotia, Ontario and Manitoba have the most restrictive programs, vaccinating only one grade of girls but Prince Edward Island, Nova Scotia and Ontario initiated their program one year earlier in 2007 thus capturing an additional age group of girls.

### TABLE 2 Provincial and Territorial HPV Vaccination Programs

<table>
<thead>
<tr>
<th>Prov.</th>
<th>Year Implemented</th>
<th>On-going Female Cohort Immunized</th>
<th>Short-term Catch-Up of Female Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>NL</td>
<td>2007-08</td>
<td>Grade 6</td>
<td>Grade 9, 2008-10</td>
</tr>
<tr>
<td>PEI</td>
<td>2007-08</td>
<td>Grade 6</td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>2007-08</td>
<td>Grade 7</td>
<td></td>
</tr>
<tr>
<td>ON</td>
<td>2007-08</td>
<td>Grade 8</td>
<td></td>
</tr>
<tr>
<td>NB</td>
<td>2008-09</td>
<td>Grade 7</td>
<td>Grade 8, 2008-09</td>
</tr>
<tr>
<td>PQ</td>
<td>2008-09</td>
<td>Grade 4 – receive 2 doses and a third dose in Grade 9</td>
<td>Grade 9 catch-up (receive all three doses) Under 18 may also receive free vaccine from their doctor</td>
</tr>
<tr>
<td>MB</td>
<td>2008-09</td>
<td>Grade 6</td>
<td>Grade 7, 2008-09</td>
</tr>
<tr>
<td>SA</td>
<td>2008-09</td>
<td>Grade 6</td>
<td>Grade 9, 2009-12</td>
</tr>
<tr>
<td>AB</td>
<td>2008-09</td>
<td>Grade 5</td>
<td>Grade 9</td>
</tr>
<tr>
<td>BC</td>
<td>2008-09</td>
<td>Grade 6</td>
<td>Grade 9</td>
</tr>
<tr>
<td>YU</td>
<td>2008-09</td>
<td>Grade 5</td>
<td>Grade 6 and 7, 2008-09</td>
</tr>
</tbody>
</table>

Source: Public Health Agency of Canada, Publicly Funded Immunization Programs in Canada—Routine Schedule for Infants and Children (including special programs and catch-up programs), Updated May 13, 2008, available online at www.phac-aspc.gc.ca/im/ptimprog-progimpt/table-1-eng.php

Table 3 illustrates the percentage, as per Statistics Canada data, of the female population aged 9 to 17 years in 2007 (the year the vaccine was introduced) that will be included in the provincial/territorial vaccination programs. Note that participation in the vaccination program is voluntary; these numbers represent eligibility, not actual immunization and assume that the programs will continue beyond the three year federal funding allocation.

Quebec offers the most comprehensive program, eventually available for 100 per cent of the target population, while Manitoba will include only 32 per cent, followed by Prince Edward Island with 41 per cent, Saskatchewan with 42 per cent and the Yukon Territory

### TABLE 3 FEMALEs ELIGIBLE FOR VACCINATION PROGRAM AND INCIDENCE OF CERVICAL CANCER

<table>
<thead>
<tr>
<th>Province/Territory</th>
<th>QC*</th>
<th>ON</th>
<th>BC</th>
<th>NL</th>
<th>AB</th>
<th>NB</th>
<th>NS</th>
<th>YT</th>
<th>SA</th>
<th>PEI</th>
<th>MB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of females 9–17 included in the program**</td>
<td>100</td>
<td>66</td>
<td>65</td>
<td>63</td>
<td>54</td>
<td>53</td>
<td>53</td>
<td>43</td>
<td>42</td>
<td>41</td>
<td>32</td>
</tr>
<tr>
<td>Estimated Annual Incidence of Cervical Cancer per 100,000 females***</td>
<td>6</td>
<td>7</td>
<td>6</td>
<td>7</td>
<td>10</td>
<td>8</td>
<td>11</td>
<td>N/A</td>
<td>8</td>
<td>10</td>
<td>7</td>
</tr>
</tbody>
</table>

*There is no school-based program for females 15 to 18 years of age, but these females may receive the vaccine free from their doctor.
** Calculated using 2006 Statistics Canada Population Data
with 43 per cent included in their programs.

Table 3 also lists the estimated incidence of cervical cancer per 100,000 females in each province based on 2008 Canadian Cancer Statistics (data not available for the Yukon Territory). The inclusion of this data provides a comparison of the relationship between the incidence of cervical cancer by province and the rate of vaccination for the target population of females aged 9 to 17 years. There appears to be no relationship between the programs being implemented in each province and the rate of cervical cancer in that province.

**Coverage Rates**

In addition to examining the programs being offered, it is important to consider the vaccine uptake or coverage rate in each province and territory to determine the effectiveness of the vaccine programs. In the first year of the program, Newfoundland achieved an 85 per cent coverage rate and the rate for the Atlantic Provinces was approximately 80 per cent. Ontario achieved a coverage rate of 53 per cent for the first dose.2 Quebec achieved a coverage rate of 84 per cent for grade 4 and 87 per cent for grade 9 for the first dose.3

**Safety of the Vaccine**

Safety of the vaccine along with religious beliefs may be factors that would impact overall uptake of the vaccine. Although these factors have not been accounted for in this article, it is worth mentioning that in Canada, as of December 31, 2008, the Public Health Agency of Canada (PHAC) has received 321 reports of adverse events, the majority of which have been minor such as injection site reactions. There has been a single report of Guillain-Barre Syndrome, a rare disorder that causes muscle weakness.4

**Cost Considerations**

The national cost of the vaccination program for one age group between the ages of 9 and 18 (representing approximately 200,000 females based on 2006 Statistics Canada data) is estimated to be $80 million, based on an average vaccine cost of $400 for three doses). This estimate does not include the costs of administering the vaccine or associated public education programs.

According to a recent Canadian study, vaccinating 12-year-old girls at a cost per course of $400, and assuming a 95 per cent efficacy with no waning of protection, the cost would be $21,000 to gain one quality adjusted life year (QALY). Estimations of results were shown to be most sensitive to age at vaccination, duration of vaccine protection, vaccine cost and QALY’s lost due to genital warts, and were least sensitive to medical costs. The study concluded that vaccinating adolescent girls against HPV is likely to be cost-effective.5

A QALY (quality adjusted life year) is defined as a year of life adjusted for its quality or its value. A year in perfect health is considered equal to 1.0 QALY. The value of a year in ill health would be discounted. For example, a year bedridden might have a value equal to 0.5 QALY.6 QALYs provide a common currency to assess the extent of the benefits gained from a variety of health interventions. When combined with the costs of providing the interventions, cost-utility ratios result; these indicate the additional costs required to generate a year of perfect health (one QALY).7

Studies are also available from other countries providing cost-effectiveness models for use of the HPV vaccine.3

**The Magnitude of HPV Infection as a Health Hazard**

In Canada, there are approximately 1,400 new cases and 400 deaths from cervical cancer each year.8 In addition to causing cervical cancer, HPV 16 and 18 infections are the primary cause of anal, penile, vaginal, and vulvar cancers and have been observed among an increasing fraction of head and neck cancers. HPV 6 and 11 infections are the primary cause of anogenital warts and recurrent respiratory papillomatosis.9 Extrapolating from recent estimates in the United States in 2007, approximately 50,000 men and women in Canada have been diagnosed with anogenital warts.10 The vaccine has been shown to reduce the risk of anogenital warts and pre-cancerous lesions by 90 per cent in men.11 An application to the FDA for approval for use in males was filed in late December 2008.

**Discussion**

The federal allocation of $300 million over three years on a per capita basis provided the provinces and territories with an equal opportunity to design and implement a vaccination program for young females. This begs the question: why are the vaccination programs across the provinces so varied with some provinces implementing a program that only covers one age group of females, while others are covering a second age group as a catch up and including all females under the age of 18?

Newfoundland, for example, is able to implement a program with greater than 85 per cent uptake for a total of five cohorts in a three year period while Ontario will cover only three age groups with an uptake estimated at 53 per cent for the first year.

Our research also reveals that the vaccination programs bear no relationship to the risk of cervical cancer in each jurisdiction. For example, Quebec and BC with the lowest incidence rate of cervical cancer at six per 100,000 females, have two of the best programs capturing 100 and 65 per cent of females aged 9–17 years, respectively. Provinces with the highest incidence rates such as Nova Scotia with only 11 and Prince Edward Island with 10 cases per 100,000 females are only capturing 53 and 41 per cent of females in their programs. If not on incidence, on what basis were program decisions made?
The question arises whether to vaccinate males. The vaccine is not currently approved for use in men in Canada or the US. It is licensed for use in males aged 9 to 15 in Europe and Australia. In these jurisdictions, males are not included in the public program but can be vaccinated at their own cost. In the UK, the vaccine is being given to homosexual men “off-label” to help protect against genital warts, anal and penile cancers.12

What role should the family physician play in the HPV vaccination program? The recommendations listed in table 1 represent the standard of care for vaccinating against HPV. Therefore, it is the responsibility of each family physician to recommend that females between the ages of 9 to 26 who will not be included in the public vaccine program be vaccinated, and to inform parents of the advantages and risks of vaccinating their daughters who are eligible for the public programs.

While it is commendable that the provinces and the Yukon Territory have initiated HPV vaccination programs, CACC recommends that cervical screening continue to be offered and promoted as a necessary component of a cervical cancer prevention program.

Conclusions
We have repeatedly observed large differences in cancer screening, care delivery and mortality between provinces. This is the first time we have been able to document the same inter-provincial variability as it relates to cancer prevention through vaccination. In this case, Quebec’s program offers the broadest coverage.

The differences in each provincial program may eventually result in differences in effective control of cervical cancer and the other diseases prevented by the vaccine in that province. These differences will not be known for several years.

The examination of Provincial/Territorial HPV vaccination programs may be an area of interest for the Canadian Partnership Against Cancer—Primary Prevention Action Group, to help determine the most effective programs moving forward in reducing the risk of cervical cancer and other HPV-related diseases.

Recommendations
• Additional research should be conducted to determine how health care system programs such as cervical screening and follow-up will be impacted by the introduction of the vaccine.13
• Research regarding vaccinating males should be monitored to determine whether it would be effective in:
  • controlling other conditions caused by HPV such as anal and penile cancers, ano-genital warts, and head and neck cancer, and
  • further reducing HPV-related diseases in the female population, since it appears that males are among the vectors carrying the virus

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