

Recommendations for Human Papillomavirus (HPV) Vaccine Schedule

Provincial Infectious Diseases Advisory
Committee (PIDAC)

Public Health Ontario

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Suggested Citation

Ontario Agency for Health Protection and Promotion (Public Health Ontario), Provincial Infectious Diseases Advisory Committee. Recommendations for human papillomavirus (HPV) vaccine schedule. Toronto, ON: Queen's Printer for Ontario; 2015.

Public Health Ontario acknowledges the financial support of the Ontario Government.

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ISBN: 978-1-4606-5816-1

Acknowledgements

This document was prepared by Shelley Deeks and Shalini Desai and builds upon work undertaken by the National Advisory Committee on Immunization. The document has been approved by the Provincial Infectious Diseases Advisory Committee on Immunization (PIDAC-I). PIDAC would like to acknowledge the expertise of the committee that contributed to this document.

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Introduction

Since the 2007-2008 school year, Ontario has had a publicly-funded, school-based human papillomavirus (HPV) immunization program for girls which uses the quadrivalent vaccine, Gardasil®. The Ontario program is locally administered by its 36 public health units. Grade eight girls (approximately 13 years of age) are eligible for publicly-funded vaccines using a three-dose schedule administered over a six month period. The provincial program targets a single grade cohort; however, if a grade eight girl has not received the vaccine, she is currently eligible to complete the series until the end of her grade 12 year.

The quadrivalent HPV vaccine, Gardasil®,¹ was authorized for use in Canada in 2006 and the bivalent vaccine, Cervarix™,² was approved in 2010. There have been three National Advisory Committee on Immunization (NACI) statements pertaining to HPV vaccines, published between 2007 and 2015.^{3,4,5} The most recent NACI statement provided recommendations for the optimal HPV immunization schedule in Canada, focusing on the number of doses required for completion of the HPV vaccine series by age.⁵ This update was prompted by accumulating evidence regarding immune response following two-dose HPV vaccine schedules, global recommendations for a two-dose schedule among immunocompetent females under 15 years of age by the World Health Organization's Strategic Advisory Group of Experts (SAGE), and approval of a two-dose schedule (0, 6 months) in girls 9 to 14 years of age at the time of first injection for Cervarix™.^{2,6,7} Subsequent to the initiation of this update, Gardasil® was also approved for use as a two-dose schedule.¹

Objective

The objective of this report is to highlight the recommendations from the 2015 update on the recommended HPV vaccine immunization schedule produced by NACI within the context of Ontario's HPV vaccination program and the vaccines' product monographs, in order to provide a PIDAC-I position on two-dose schedules. Duplication of details contained within the NACI update have been avoided and the reader is referred to the NACI statement for further information.⁵

Summary of the NACI recommended Human Papillomavirus (HPV) vaccine immunization schedule for females

In the 2015 NACI update on the recommended HPV vaccine immunization schedule, there were three recommendations pertaining to females. These recommendations and their corresponding evidence grade are reprinted here.⁵

Healthy females (9-14 years of age) – NACI Grade A Recommendation

Either a 2-dose or 3-dose schedule of the HPV vaccine (Gardasil® or Cervarix™) is recommended for immunocompetent, non-HIV infected females 9-14 years of age. For a 2-dose schedule, at least 6

months between the first and second dose is recommended. If the interval between doses is shorter than 5 months, a third dose should be given at least 6 months after the first dose.

Healthy females (≥ 15 years of age) – NACI Grade A Recommendation

A 3-dose schedule of the HPV vaccine (0, 2 and 6 months for Gardasil[®] and 0, 1, and 6 months for Cervarix[™]) is recommended for females 15 years of age and older, unless the first dose of HPV vaccine was administered before the age of 15 years. If the first dose was administered between 9-14 years of age, a 2-dose schedule is sufficient for females ≥ 15 years of age, with the second dose administered at least 6 months after the first dose.

Immunocompromised individuals and immunocompetent HIV-infected individuals – NACI Grade I Recommendation

A 3-dose schedule of the HPV vaccine (Gardasil[®] for males and females - 0, 2, 6 months; or Cervarix[™] for females – 0, 1, 6 months) is recommended for individuals who are immunocompromised and immunocompetent HIV-infected individuals. There is insufficient evidence to recommend a 2-dose schedule in these populations; therefore a 3-dose schedule continues to be recommended for individuals who are immunocompromised and for immunocompetent HIV-infected individuals. Further study in these populations is required.

These recommendations are the result of available data on immunogenicity indicating that two doses of HPV vaccine in girls nine to 14 years of age were non-inferior to both three doses in the same age group or three doses in females aged 15-24 years. It was noted that a schedule with fewer doses and similar effectiveness would be more acceptable to both vaccinators and the public, and would also likely have a beneficial impact on vaccine coverage and safety.⁵

Legal considerations: authorized age indication

Currently both of the available HPV vaccines are authorized for use as either a two- or three-dose schedule, depending on the age at first administration. Cervarix[™], is authorized for use in Canada as a two-dose schedule (0, 6 months) for girls 9 to 14 years of age at the time of first injection (ref PM). GSK received this authorization in July 2014.² On March 10, 2015, following the publication of the NACI statement, Gardasil[®] was also approved for use in Canada using a two-dose schedule for individuals 9 through 13 years of age at either 0, 6 months or 0, 12 months.¹ It is noteworthy that the upper limit of the age that is approved as a two-dose schedule for Gardasil[®] by Health Canada is 13 years, compared to the upper age in the NACI statement which is 14 years.^{1,5} The recently approved Gardasil[®]9, or nonavalent vaccine, which protects against 5 additional genotypes compared to Gardasil[®], is authorized for use as a three-dose schedule only.⁸ NACI has not yet issued a statement on Gardasil[®]9.

Programmatic and Operational Considerations

NACI does not include economic or other programmatic considerations while formulating their recommendations. The committee indicated that provinces and territories must consider economic, legal, ethical, and political factors, as well as other local programmatic and operational factors when determining the appropriate HPV vaccine schedule to be used within their jurisdiction.

The current Ontario HPV vaccine program involves a cohort of approximately 74,000 grade eight girls (age approximately 13 years) every year. Reducing the number of doses in the HPV vaccine series would have substantial economic implications. Not only would vaccine costs be decreased by one-third, the 36 local public health units (PHUs), may be able to decrease the number of visits to the schools within their jurisdiction, resulting in additional program efficiencies. These program efficiencies could be further enhanced if the outstanding PIDAC-I recommendation of moving the HPV vaccine program from grade eight to grade seven were implemented.

There are currently three school-based public health delivered vaccination programs in the province.⁹ Two of the programs are delivered in grade seven (hepatitis B and quadrivalent meningococcal vaccination programs) and one program, requiring three visits, is delivered in grade eight for females only. Whereas hepatitis B prevention requires a two-dose series, the quadrivalent meningococcal vaccination program requires only a single dose. In Ontario, grade seven and eight students tend to attend the same school, which means that PHUs can plan their scheduled visits to immunize students in both grades. One challenge with the delivery of a three-dose HPV program in grade eight is that the student may not be present at the school during each of the scheduled immunization clinics. If this occurs, the student would need to complete the series outside of the school setting, as most will be transitioning to a different school in grade nine. Changing the HPV vaccination program to a two-dose schedule delivered in grade seven would provide more opportunity for students to receive the recommended doses, as they would still be in the same school in grade eight and could receive any missed doses in that year while the PHUs are in the school. There would be two options for delivery of the three programs in grade seven. The PHUs could schedule the visits so that they deliver vaccines at the schools twice in a school year, however three vaccines would need to be given at one of the visits. Although it is acceptable from a vaccine safety and efficacy perspective to give three vaccines simultaneously at one visit (at different injection sites), there have been some concerns raised from providers about acceptance. Alternatively, if acceptance of delivering three vaccines at one visit was a concern, the PHUs could schedule three visits in the grade seven school year, with two vaccines being delivered at each visit.

Gardasil®'s licensed age indication for a two-dose schedule is 13 years.¹ Although most individuals in grade eight are 13 years of age when they receive their first dose of vaccine, any child who is a year or more older than the typical age for that grade would not be eligible for a two-dose schedule as per the authorized indication (although they would remain eligible for a two-dose schedule under the NACI recommendation). As grade seven students tend to be 12 years of age, most of the girls in the eligible

grade cohort would also be age-eligible for the schedule based on its authorized indication.

As noted by NACI, a beneficial effect of decreasing the number of doses would include fewer HPV vaccine-related adverse events following immunization (AEFIs) occurring and being reported in the province. As each AEFI has associated workload implications at a health unit level, decreasing the total number of AEFIs without impacting the effectiveness of the vaccine program would result in program efficiencies. [Note: In 2012 and 2013, there were 46 and 40 AEFIs reported, respectively, after receipt of Gardasil® vaccine in Ontario.^{10,11}] In addition, HPV vaccine series coverage would increase, as individuals would be fully vaccinated after two rather than three doses.

Within Canada, the provinces of Quebec (grade 4) and British Columbia (grade 6) have implemented a two-dose HPV vaccine series for girls in August 2013 and October 2014, respectively. Both provinces are using Gardasil® in their publicly funded program. Other Canadian jurisdictions are considering changes in schedule for the 2015/16 school year.^{12,13}

PIDAC-I recommendation

PIDAC-I supports the recommendations made in the NACI update on HPV vaccine immunization schedule and recommends that Ontario implement a two-dose Gardasil® vaccine program in grade seven.

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