Sections

53 Questions _____ Page iV
A list of all the clinical questions by section.

HPV _______________ Page 1
Questions 1–12

Vaccines _________ Page 17
Questions 13–43

Screening ________ Page 53
Questions 44–48

Diagnosis & Follow-up _______ Page 59
Questions 49–53

Resources _________ Page 63
A resources section is included at the end of this publication to provide links to other documents, programs and guidelines relevant in Canada.
Introduction

The Society of Gynecologic Oncology of Canada (GOC) has updated its authoritative FAQ document on HPV diseases and vaccination. The intent of this update is to address the medical community’s need for education and guidance on the diagnosis and treatment of HPV-related disease, including cervical cancer screening, treatment and prevention strategies, plus HPV vaccination for both females and males.

New Information – New Update

Research and literature has evolved dramatically since GOC first published the 2007 version of Contemporary Clinical Questions on HPV Vaccination. The publication was well received with several thousand copies distributed nationwide.

Since that time, significant changes in practice have occurred. We now better comprehend HPV epidemiology, treatment and prevention of HPV-related diseases. New screening practices, introduction of a nonavalent vaccine and de-escalation of treatment for some HPV-positive (HPV+) lesions are all important milestones in treatment and prevention of HPV.

As key clinical stakeholders and leaders in the diagnosis and treatment of HPV-related disease, GOC and its members have received numerous questions regarding prevention, diagnosis, treatment and management. In response to these questions, and in recognition of the great knowledge increase in the field over the last decade, GOC is publishing this second edition, to ensure that health practitioners who deal with HPV-related disease continue to have access to the most current, evidence-based and trustworthy information.

HPV – A Growing Concern

Our understanding of the disease burden for HPV-related cancers in both men and women is growing. Today we know that cervical cancer may not be the predominant HPV-related cancer in North America. Recent data from the American Cancer Society and the Centers for Disease Control and Prevention suggest that cervical cancer accounts for only one-third of all HPV-related cancers. As research continues, the breadth of burden for HPV-related diseases widens progressively. We are learning how HPV is a causal factor for several cancers including vulvar, vaginal, penile, anal and oropharyngeal cancer (a condition which has been described as an epidemic in the USA and Canada). Recent data from the USA suggest that the annual number of HPV-related oropharyngeal cancers in men is very similar to that of cervical cancer.
(10,511 vs 11,388) and is expected to surpass cervical cancer in the next five years. Also, screening practices have changed dramatically, such as extending screening intervals to three years and the introduction of HPV testing.

**Peer-reviewed and Evidence-based**

To ensure the most accurate information and interpretation of the science, steering and scientific committees were selected for the project. The committees represented gynecologic oncologists and HPV experts from across Canada, as well as a representative from an industry partner, Merck Canada. The steering committee provided oversight of the project by: facilitating information updates about HPV science; ensuring information was presented in a clear, concise and scientifically sound format; and overseeing document development and design. The scientific committee was responsible for selecting, writing, and reviewing the scientific information contained in the document to ensure scientific accuracy.

Hundreds of questions were acquired from three different sources: a survey of Canadian health care practitioners, a medical services database from Merck, and participants who attended five scientific events. The scientific committee selected questions and formulated preliminary answers during a one-day workshop. An independent medical writer performed a thorough literature search and drafted the document. The second edition of *Contemporary Clinical Questions on HPV-Related Diseases and Vaccination* is the resulting product. It includes 53 of your most frequently asked questions, answered by leading medical experts in the field of HPV diseases.

**The Society of Gynecologic Oncology of Canada** is proud to provide two versions of the second edition of *Contemporary Clinical Questions on HPV-Related Diseases and Vaccination*. This abridged print version provides health care professionals with easy hard-copy access to information. The comprehensive online version provides greater detail regarding current evidence, data, and the full list of references; it is available on the GOC corporate website at www.g-o-c.org.

We would like to express our thanks to the scientific committee and Dr. Roberta Howlett for their contributions, and sincerely hope we have provided some clarity for clinicians on the constantly evolving clinical practice in HPV-related disease management.

James Bentley, MBChB, FRCS(C)
Co-Chair, Steering Committee

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Co-Chair, Steering Committee
List of Questions by Section

Questions 1 – 12

HPV

Q1 What is the incidence of HPV-related disease in Canada? _______________ 1

Q2 What percentage of atypical squamous cells of undetermined significance (ASCUS/ASC), ASC-H, LSIL, HSIL, squamous cell cancers and adenocarcinomas are attributable to HPV genotypes covered by the vaccines? ________________________________ 3

Q3 What is the worldwide distribution of HPV types included in the nonavalent HPV vaccine? ________________________________ 4

Q4 What is the risk of HPV-related anal cancer? _________________________ 5

Q5 What is the risk of HPV-related oropharyngeal cancer? _________________ 7

Q6 What risk and co-factors affect HPV infection, acquisition, persistence and progression to disease? ____________________________ 8

Q7 Can HPV infections become latent or dormant? ______________________ 9

Q8 Are HPV tests available in Canada and for whom are they available? How much do they cost? _______________________________________ 10

Q9 What is a concise way to discuss HPV infection with patients in the colposcopy clinic who assert that they and their partner are (and have been) monogamous? _________________________________ 11

Q10 Can two monogamous partners re-infect each other with HPV? ________ 13

Q11 Does an abnormal Pap test mean that a woman has been exposed to hrHPV? ___________________________________________ 14

Q12 Do condoms protect against HPV? _______________________________ 15
Questions 13 – 43

VACCINES

13. What are the components of the prophylactic vaccines? _______________ 17
14. Who should be vaccinated with HPV prophylactic vaccines? ___________ 18
15. Is there evidence that the vaccines work in the “real world”? ___________ 20
16. Are HPV vaccines safe and what data are available regarding vaccine side effects or adverse reactions in clinical studies and vaccine programs? __ 21
17. How is the long-term safety profile of HPV prophylactic vaccines monitored? __________________________________________ 22
18. Has there been any HPV genotype replacement since vaccine implementation? ________________________________ 25
19. Will sexually active women benefit from HPV vaccination? Will women treated for previous HPV infection and/or HPV-related cervical or genital diseases benefit from HPV vaccination? ___________________________ 26
20. Should I recommend the vaccine to males? Why are boys not included in most provincial HPV vaccination programs? ______________________ 27
21. Is the inclusion of males in an HPV immunization program cost-effective? When will HPV vaccine be funded for boys? Should male partners be vaccinated? ____________________________________________ 28
22. I hear that a new nonavalent vaccine is now available. What are the advantages and disadvantages? ______________________________ 30
23. What about the two-dose vaccination program? Is it sufficient and safe? Why has there been a two-dose vaccine program in Quebec and why are there differences across provinces and territories? ________________ 31
24. What is the benefit of vaccinating women over the age of 26 years and what studies have been done in this age group? _________________ 33
25. Should health care providers be vaccinated? __________________________ 34
26. How long does protection last with HPV prophylactic vaccines? _________ 35
27 Will a vaccine booster be necessary? ______________________________ 37
28 Will HPV vaccines protect against non-gynecological cancers? For example, do HPV vaccines protect against oropharyngeal and anal diseases related to HPV? ______________________________ 37
29 How many doses of nonavalent vaccine will be required? What is the recommended schedule? ______________________________ 39
30 Why is the uptake of HPV vaccination poor in some jurisdictions and good in others? ______________________________ 39
31 With the availability of the new nonavalent HPV vaccine, should I defer recommending HPV vaccination until it is clinically available? ________ 40
32 How do you complete immunization if the recommended schedule is interrupted? If a patient delays the third vaccine dose, how long is too long? ______________________________ 41
33 Does the vaccine have to be refrigerated if not used immediately? ________ 41
34 When the new nonavalent vaccine is available, should women who received the quadrivalent vaccine receive a booster with the nonavalent vaccine? ______________________________ 42
35 What are the contraindications to HPV vaccination? ______________________________ 43
36 Should pregnant or lactating women be vaccinated with HPV prophylactic vaccines? How soon after giving birth can a mother be vaccinated? ______________________________ 44
37 Can HPV prophylactic vaccines be given concomitantly with other vaccines? ______________________________ 45
38 Can HPV prophylactic vaccines cause HPV-related diseases in immunized or immunocompromised individuals? ______________________________ 46
39 Will prophylactic HPV vaccines help treat established current HPV infection or slow the progression to cancer pre-curors? ______________________________ 47
40 How do bivalent, quadrivalent and new nonavalent HPV vaccines differ? ________ 48
41 Does a patient have protection if only part of the recommended vaccination protocol is completed? ______________________________ 49
42 Will HPV vaccines protect against other HPV types, i.e., will they offer cross-protection? What is cross-protection? ________ 50
43 Should HPV testing be done before vaccination? ______________________________ 51
Questions 44 – 48

SCREENING

Q44 Will prophylactic HPV vaccination reduce or eliminate the need for cervical cancer screening? ____________________________ 53

Q45 Will an HPV test replace current screening by Pap tests? If so, how will we screen? _______________________________________ 54

Q46 What is the best way to screen young women who have been vaccinated? ________________________________ 55

Q47 Is HPV testing recommended in men? _____________________________ 56

Q48 Is there a role for anal screening and anoscopy? _________________ 57

Questions 49 – 53

DIAGNOSIS & FOLLOW-UP

Q49 How do you get HPV-related oral disease? Is there any indication to screen for oral HPV or associated disease? ____________________________ 59

Q50 What is the best test of cure after treatment for cervical dysplasia? _______ 59

Q51 How should the clinician treat those who are persistently positive for oncogenic HPV? ______________________________ 60

Q52 If patients have had SIL/CIN and been treated by LEEP, will they still have the virus? Can they transmit it to their partners? Will their partners re-infect them each time they have sexual contact? Does vaccination help? ____________ 61

Q53 Should a person whose partner has had genital warts have an examination of the oral cavity and throat by an ear, nose and throat (ENT) specialist? __ 62
What is the incidence of HPV-related disease in Canada?

- Cervical cancer accounts for about one-third of HPV-related cancers with 1,450 new cases and 400 deaths per year in Canada. For every case of cancer, thousands of additional women have precancerous lesions that often require interventional procedures.

- HPV-related oropharyngeal cancers have increased significantly in the past few decades, especially in men, whose rates are thought to approach those of cervical cancer.

- Anogenital warts represent the largest burden of non-oncogenic HPV disease.

- Recurrent respiratory papillomatosis is rare, but confers very high morbidity on children, who often require several surgeries each year to clear blocked airways.

Evidence regarding the incidence of HPV-related disease has expanded significantly over the past ten years. HPV-related diseases are now better understood to affect both women and men in the form of anogenital warts, and as cancers of the cervix, anus, vulva, vagina, penis, oral cavity and oropharynx.

HPV is a very common virus and virtually all who are, or have ever been, sexually active will acquire the virus at some point, often shortly after first sexual activity. HPV is spread primarily through sexual activity, either skin-to-skin or skin-to-mucosa, even without penetration. Most people clear the virus within one to two years. In some individuals who are more susceptible, the virus is not cleared and HPV infection(s) will persist, thereby increasing a person’s risk of developing precancerous lesions. Lesions are categorized as low- or high-grade. Low-grade lesions are generally not treated, but do require follow-up. High-grade lesions require treatment and follow-up.
### Table 1: Average annual number of cases and age-standardized incidence of HPV-associated cancers among persons aged 15 years and older in Canada (1997–2006) and estimated attributable proportion due to HPV.

(Excerpted and adapted from NACI Guidelines)

<table>
<thead>
<tr>
<th>Sex</th>
<th>Anatomical site</th>
<th>Average annual incidence / 100,000</th>
<th>Average annual number of cases</th>
<th>Estimated attributable HPV proportion (%)</th>
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<tr>
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<td>Any type</td>
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<tr>
<td><strong>Males</strong></td>
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<tr>
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<td>3.7*</td>
<td>471.3</td>
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<tr>
<td><strong>Females</strong></td>
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Detailed references for Q1 (1, 6–24) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.
What percentage of atypical squamous cells of undetermined significance (ASCUS/ASC), ASC-H, LSIL, HSIL, squamous cell cancers and adenocarcinomas are attributable to HPV genotypes covered by the vaccines?

- 90% of cervical cancers and up to 85% of abnormal cytologic lesions are related to HPV genotypes covered by the vaccines.

**For cervical cancer**, the distribution of HPV types is fairly uniform worldwide, with 70% to 80% of cases due to types 16 and 18. Another 10% to 20% are due to types 45, 31, 32, 58, 52 and 35. For pre-cursor lesions, the data demonstrated a common trend of decreasing incidence of HPV 16 and 18 with less severe histology, i.e., HPV 16 is more common in CIN3 than CIN1. Table 2 in the comprehensive version demonstrates this trend, as found in a Canadian study by Coutlée et al (2012).

**For HSIL**, most cases are caused by HPV types 16, 31, 58, 18, 33, 52, 35, 51, 56, 45, 39, 66, and 6 (in order of decreasing prevalence).

**For LSIL**, the average proportion of women testing positive for HPV (HPV+) ranged from 59.1% in four studies in Africa to 80.1% in 13 North American studies. Type 16 was the most common, found in 26.3% of HPV+ cases worldwide. Type 18 was found in 8.6% of HPV+ cases. Other types included 31, 51, 53, 56 and 52.

**For ASCUS/ASC cytology**, HPV positivity varies with age. In the ASCUS/LSIL Triage Study (ALTS), 61% of cases tested positive for HPV. In HPV+ ASCUS cases, the baseline prevalence of HPV 16 was 24% and the prevalence of HPV 18 was 8%. Proportions varied with age, with HPV 16 and 18 present in 35% of women with HPV+ ASCUS aged 18–24, and in 19% of women over 35 years.

Seoud et al (2011) reported that HPV types 16, 18 and 45 were associated with about 90% of adenocarcinoma cases worldwide. Similarly, a recent analysis of 760 cases from around the world reported that 94.1% of adenocarcinoma cases were attributable to the same three high-risk HPV (hrHPV) types. Pirog et al (2014) concluded that prophylactic vaccines against HPV 16 and 18 may prevent up to 82.5% of potential adenocarcinoma, and the
The nonavalent vaccine prevents pre-cancerous infection with HPV types 16 and 18 (70% of cervical cancers) as well as HPV types 31, 33, 45, 52, and 58 that account for about 20% of additional cervical cancers.

As with the quadrivalent vaccine, the nonavalent vaccine also prevents anogenital warts related to HPV types 6 and 11.

A recent IARC Monograph illustrates the crude prevalence of HPV types around the world based on a meta-analysis of data from 36 countries, including 157,879 women with normal cytology. In every jurisdiction with available data, HPV 16 was the most common. Worldwide overall crude prevalence was 10.0%; the top five HPV types were HPV 16 (2.6%), 18 (0.9%), 58 (0.9%), 52 (0.9%) and 31 (0.6%). According to a meta-analysis by Bruni et al (2010), global HPV prevalence was about 11.7% based on data from 194 studies that included over one million women with normal cytology. Where HPV data was available (n = 215,568), the most common types around the world were HPV 16 (3.2%), 18 (1.4%), 52 (0.9%), 31 (0.8%), and 58 (0.7%).

In general, hrHPV prevalence and infection is highest among teens and young adults. Testing positive for hrHPV is not necessarily indicative of transient or persistent HPV infection. In men, HPV infections are also frequent, but prevalence varies considerably according to geographical region, anatomical site, sampling technique and method of detection. Contrary to the case of women, HPV prevalence in men varies much less by age, and rates stay relatively constant up to an advanced age.

In studies in Ontario (Sellors et al, 2000) and Nunavut (Healey et al, 2001), prevalence of HPV infection was higher among all age groups in Nunavut than in Ontario, ranging from 42% among women under 20 years to 15% among
women over 40 years. Prevalence in Ontario in the same age groups was 16% and 7%, respectively. Data from British Columbia (Ogilvie et al, 2013) revealed an overall rate of 12.2% in a population-based sample of HPV-positive cervical specimens from 4,330 participants collected between June 2010 and February 2011. The highest prevalence of hrHPV was noted among the youngest age groups: ages 15–19: 25.7%; 20–24: 33.2%; 25–29: 21.9%; 30–34: 12.6%; 35–39: 9.5%; 40–44: 8.4%; and >45: 3.4%. HPV 16 was the most common genotype.

From Quebec, Dr. Goggin et al (2015) presented early results from the Pixel study at the EUROGIN meeting in February 2015. The study collected specimens from almost 3,600 participants in Quebec, including about 2,000 women (18–29 years), who self-reported their immunization status. Overall, 35.4% tested positive for HPV. The most common HPV types were 51, 59, and 52. HPV 16 was less common, but frequency increased with age. Those HPV types that are included in preventive vaccines were found less frequently in this study of Quebec women compared to unvaccinated women (of the same age) in the general Canadian population.

Detailed references for Q3 (12, 38–45) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

**Q4 What is the risk of HPV-related anal cancer?**

- The incidence of HPV-related anal infections and anal cancer is increasing in developed countries.
- Infections are less likely to clear among those with more lifetime sexual partners, those who engage in receptive anal intercourse, those who smoke, and those who are HIV+.
- Most cases of anal intraepithelial neoplasia (AIN2/3 (95.3%) and anal cancer (88.3%) are related to HPV, most often types 16 (75.4%) and 18 (3.6%).
- The quadrivalent and nonavalent vaccines are indicated for the prevention of anal cancer and AIN.

A recent analysis from 23 countries reported that HPV DNA is found in 88.3% of anal cancers and in 95.3% of AIN2/3 cases. The most frequent HPV type in cancer and AIN2/3 was type 16 (75.4%). HPV 18 was the next most common at 3.6%. Alemany et al (2015) concluded that HPV is very likely a necessary cause of anal cancer in women and men.
Research from developed countries such as Canada, Australia, UK, USA and Denmark demonstrate that anal cancer is increasing among both women and men. In fact the rates have doubled over the past three decades. Among women, the rate of anal cancer in Alberta doubled from 1975 to 2009 increasing from 0.7 per 100,000 to 1.5 per 100,000, with an annual percentage change (APC) of 2.2. The increase in incidence was highest among those under 45 years, with an APC of 5.3, and those from 45–54 years, with an APC of 6.4. Incidence decreased with advancing age. Similarly, anal cancer in men increased from 0.5 per 100,000 in 1975 to 0.9 per 100,000 in 2009, with an APC of 1.8. Among men, incidence per five-year intervals increased in all age groups, with the APC ranging from 1.8 in the 45–54 and 55–64 age groups, to 3.8 among those younger than 45 years at diagnosis.

For men who have sex with men (MSM), the rate of anal cancer is very high at 35 per 100,000. It should be noted that this rate approximates the rate of cervical cancer prior to the introduction of routine screening among women in the general population. The rate in HIV-positive (HIV+) men is even higher. A recent US study found the rate of anal cancer in the HAART (highly active anti-retroviral therapy) era to be 137 per 100,000. The increased rate has been attributed to the increased survival of individuals on HAART, which allows sufficient time for HPV-related anal dysplasia to develop into malignancies.

Risk of anal cancer rises with increased number of sexual partners, receptive anal intercourse, history of HPV-related anogenital diseases, smoking and HIV infection.

The quadrivalent and nonavalent vaccines are indicated for the prevention of anal cancer and AIN. As most anal cancers are associated with HPV 16 and 18, expert opinion suggests that the bivalent vaccine would also be highly effective.

Detailed references for Q4 (2, 17, 21, 46–51, 252–254) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.
What is the risk of HPV-related oropharyngeal cancer?

- HPV-negative (HPV-) oropharyngeal cancers are generally found in older individuals with a history of smoking and/or alcohol use.
- HPV-positive (HPV+) oropharyngeal cancers tend to present in younger patients, who seldom have a history of smoking and/or alcohol use.
- The risk of HPV+ oropharyngeal cancer has increased dramatically in many developed countries over the past few decades, particularly among men with a lifetime history of more oral and vaginal sex partners.
- Husbands of women with cervical cancer have twice the risk of oropharyngeal cancer.

Rates of oropharyngeal cancer vary significantly by geographical region. HPV- cancers are more common in regions with high rates of smoking. HPV+ cancers are more likely, and in fact are increasing, in regions where smoking rates have decreased. In the USA, HPV+ oropharyngeal cancer increased by 225% from 1988 to 2004 and is expected to surpass cervical cancer rates by 2020.

Reports from Canada indicated similar findings with rates more than doubling in Alberta from 1975 to 2009, and in Ontario between 1993–1999 and 2006–2011. Rates were higher among men than women. A Canadian report found that rates of HPV+ oral squamous cell carcinoma (HPV+ OSCC) increased in men from 2.5 to 4.1 per 100,000 from 1992 to 2009, and in women, from 0.7 to 1.1 per 100,000 over the same time period.

HPV+ OSCC is related to oral sex. A study from Johns Hopkins found an association between HPV+ OSCC and the number of oral sex partners. Most men (85.4%) and women (83.2%) reported having performed oral sex. Men had more lifetime oral and vaginal sexual partners ($p < 0.001$), and HPV 16 was higher in men than in women ($p < 0.001$). Younger people were more likely to have reported engaging in oral sex. In addition, work by Hemminki et al (2000) found that husbands of cervical cancer patients were twice as likely to present with oropharyngeal cancer.
Recent studies suggest that HPV- head and neck SCC is associated with older age, use of tobacco and alcohol, and lower socio-economic status. Whereas, HPV+ cancers are associated with younger age at presentation, sexual behaviour and higher socio-economic status. A recent British Columbia study found that the lowest socio-economic status was associated with an increased risk for all oropharyngeal cancers; however, that study did not differentiate between HPV+ and HPV- oropharyngeal cancers.

In an Ontario study, HPV+ individuals experienced markedly improved recurrence-free overall survival (recurrence-free survival: 82% vs. 53%; overall survival: 83% vs. 37%; \(p < 0.0001\)) (Nichols et al, 2013).

Detailed references for Q5 (17, 18, 20, 21, 52–64) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

q6 What risk and co-factors affect HPV infection, acquisition, persistence and progression to disease?

- Factors that influence HPV persistence and progression include number of sexual partners, individual immune state (immunosuppression), smoking, use of oral contraceptives, and history of infection with other sexually transmitted pathogens.

- Ongoing or future epidemiological studies will shed more light on the relative importance of these co-factors.

Most HPV-related infections are transient and clear spontaneously; however, those that persist may gradually progress to high-grade intraepithelial neoplasia and/or cancer. Lifetime number of sexual partners is the main determinant of anogenital HPV infection in both men and women. Winer et al (2012) studied women aged 25–65 who participated in online dating. In this study, age did not correlate with acquisition; rather, acquisition was directly related to new partners. Therefore, those who have, or are planning to have, new sexual partners are at risk for HPV acquisition. Other co-factors include immunosuppression, smoking and oral contraception.

A recent study reported that using oral contraceptives for five years or longer conferred a two-fold additional risk of cervical cancer; the risk levelled off after discontinuation and evened out after 10 or more years. Among women who tested positive for oncogenic HPV, current smokers were two and one-
half times more likely to present with CIN3 (95% CI: 1.8–3.6), compared to non-smokers. In a large European study (n = 308,036), Roura et al (2014) reported that smoking status, duration and intensity doubled the risk of progression to CIN3, carcinoma in situ and invasive cervical cancer. Conversely, quitting for 10 years decreased the risk of progression by half.

The type of sexual activity can also influence the site of acquisition. Although HPV anal infection is common in men and women who report never having receptive anal intercourse, rates of infection and disease are higher in those who have. People with more oral sex partners have a higher risk of oropharyngeal infection and cancer than those with fewer partners.

Detailed references for Q6 (6, 13, 39, 40, 58, 64–73, 260–264) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

Q7 Can HPV infections become latent or dormant?

- Evidence for the possibility of a latent or dormant state of HPV is unclear and incomplete; however, there is indirect support for latency (i.e., a non-infective state).

- Recent studies and commentary regarding the risk of reactivating previous HPV infection among those with autoimmune diseases, or suppressed/compromised immune systems, highlight the need for further study regarding implications for current and future generations.

After initial clearance of the lesion, a period of viral latency is likely, during which HPV persists below levels that can be detected by current assays. The virus remains latent in the basal cell layers of the mucosa and skin. At this point, the virus is not clinically infectious and the individual is asymptomatic.

Indirect evidence for this comes from the work of Steinberg, who showed that HPV could persist in certain tissues for years without causing clinical diseases. In addition, Broker and colleagues (2001) observed that women who appeared to be HPV- before receiving an organ transplant were HPV+ after the transplant and treatment with immunosuppressive agents. This implies that an intact immune system is necessary for the virus to remain in a state of latency. However, factors that regulate viral persistence and events that lead to latency are poorly understood.
The issue is unclear as to whether a new lesion results from re-activation or from a new infection. Most women (80%) who become infected with a specific HPV type can later show no evidence of that type. It is generally thought that later re-infection with the same type is uncommon.

Gravitt (2012) reviewed the literature on latency and concluded there is strong evidence, albeit circumstantial, for HPV latency. Transplant patients and HIV-positive individuals are at higher risk of re-activation, and there is growing evidence of HPV re-activation in older people. Gravitt asserted that re-activation risk would be proportionate to the total burden of past HPV infection.

Detailed references for Q7 (6, 74–82) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

8 Are HPV tests available in Canada and for whom are they available? How much do they cost?

- Yes, tests are available, but there is considerable diversity across Canada as to their availability, purpose of use, and cost.

This is a dynamic area with emerging evidence and policy change. Individuals should consult their health care provider as to its appropriateness. HPV tests determine whether a specimen is positive for one or more of the HPV types contained in the assay. Genotyping is necessary to identify which hrHPV type(s) accounts for a positive reading. In some parts of Canada, HPV testing is recommended as a triage test to complement cervical cytology. In some cases, it is recommended as the primary screening test. Validated tests are also used within institutions for research, but have not been approved by Health Canada.

Some jurisdictions in Canada fund the cost of the test for specific use(s) but the costs are not covered everywhere. The cost can be about $80 on a patient-pay basis. It may also be covered under private insurance plans. HPV testing is also used in some regions to clarify diagnosis and/or inform treatment outcomes and options.
Health Canada has approved two HPV tests:

A. Hybrid Capture (Digene’s HC2 Test)
   a. HR: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68
   b. LR: 6, 11, 42, 43, 44

B. Roche
   a. HR: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
   b. genotype specific - HPV 16 and HPV 18

What is a concise way to discuss HPV infection with patients in the colposcopy clinic who assert that they and their partner are (and have been) monogamous?

- HPV infection is very common and most women will have an HPV infection at some time during their life.
- HPV is very easily transmitted and does not require sexual intercourse.
- Having an infection does not necessarily mean that you or your partner have had other partners.

**Normalize and de-stigmatize the topic**

HPV infection is very common and most women will have an HPV infection at some time during their life. HPV is easily acquired and transmitted. Even without sexual intercourse, HPV can be spread through hand-to-genital, oral-to-genital, and genital-to-genital contact, as well as by vertical transmission.

**Put it into context**

Most infections will clear spontaneously without any negative effects. If the infection does not clear, it can cause cell changes in the cervix that show up on a Pap test.
Provide relevant information

We do not fully understand clearance of HPV and so we cannot predict in whom, how, or when the infection will clear. Persistent infection with the same genotype can lead to precancerous lesions that, if undetected or untreated, can lead to cancer. Most cervical and other HPV-related cancers develop slowly. Screening strategies, which may or may not include HPV testing, are effective. When abnormalities that could become malignant are detected, they can almost always be treated successfully. Disease is a rare consequence of a common infection.

Provide reassurance

- “It is impossible to tell where it came from; having an infection does not necessarily mean that you or your partner have had other partners recently.”

- “The HPV virus is almost always transmitted by any kind of intimate skin-to-skin contact and/or sexual activity (even without penetration). You or your partner may have had this infection in the distant past; it may have been dormant and only recently reactivated. So even if you are both monogamous, the infection may have come back.”

- “However, our current focus is on getting you better from this infection and only treating disease that has potential to cause you harm, i.e., pre-invasive diseases. HPV is not a disease, but rather an infection; CIN3+ is a disease.”

Educate

You are an important source of reliable information. If your province or territory has provided health promotion materials, share these with your patients because they will frequently have questions after they leave your office. Also, refer them to one or more of the many reliable and evidence-informed websites in the Resources section at the end of this book.

Map out a strategy to keep the patient safe

- Reduce patient risk.

Talk about risk reduction (if risk exists); encourage the use of condoms; promote effective screening strategies; encourage timely follow-up regarding diagnostic and/or treatment steps; and recommend immunization when applicable.

NB: You are the most important source of evidence-based information for your patients. They rely on you to provide accurate and current information and make the best recommendations.
Can two monogamous partners re-infect each other with HPV?

- It is generally accepted that HPV is passed between sexual partners.

- Previously, the most commonly held belief was that infection and subsequent clearance of an HPV type protected a person against re-infection with the same type. However, we now know that individuals can become re-infected and develop disease from a type that had previously cleared.

- Condoms can offer some protection against HPV infection; however, one study showed that transmission still occurred even when condoms were reportedly used 100% of the time.

Yes, it is clear that HPV is passed between sexual partners. If a partner is infected prior to initiation of a monogamous relationship, transmission can occur. During a relationship, the infected partner may transmit infection(s) at, or shortly after, initiation of sexual activity. Theoretically, an HPV virus could reactivate several years later, and allow transmission to the current partner at that time (Brown et al, 2005). If neither partner has ever been exposed to, and never encountered the virus during the relationship, then transmission will not occur.

Among all viruses causing sexually transmitted infections, HPV is one of the easiest to transmit via skin-to-skin contact, even without penetration. Based on computer modelling, the probability of transmission per act of intercourse is estimated at approximately 40%, and can range from 5% to 100%. This risk of transmission is several times higher than that of other viral sexually transmitted infections, e.g., HIV or herpes simplex virus 2.

One transmission study reported that concordance of HPV is high in heterosexual couples, ranging from 60% to 80%. Burchell et al (2011) assessed HPV transmission in newly formed heterosexual couples in Quebec. At enrolment, couples were discordant for one or more HPV types. Among 73 couples, transmission was noted at follow-up. Most (83.6%, 61/73) involved transmission of a single HPV type and 13.7% (10/73) involved transmission of two types. Clearance of an HPV type primes the immune
system to protect against future exposure; however, this level of protection is not complete as individuals can be reinfected by, and develop diseases from, the same HPV type.

Detailed references for Q10 (6, 75, 80, 83–87, 89–92) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

**Q11 Does an abnormal Pap test mean that a woman has been exposed to hrHPV?**

- Yes, most women with an abnormal Pap test have hrHPV infection, although it can vary by Pap test results and age.
- Pap tests are used to detect disease; they do not test for HPV infection.
- HPV infection can cause abnormal Pap test results. Low-grade lesions may be associated with other factors, including atrophy; high-grade lesions are more likely related to hrHPV.
- In the case of ASCUS/ASC, 50% of women test positive for hrHPV DNA.
- In the case of ASC-H, over 70% of women with abnormal Pap tests are positive for hrHPV.

The purpose of the Pap test is to detect abnormal cervical cells that may indicate disease. Although HPV infection can cause abnormal Pap test results, the Pap test is not a test for HPV infection. Most HPV infections are transient and will not lead to abnormal test results. In 50% of women with newly acquired HPV infection, HPV DNA cannot be detected after approximately one year; 90% of infections clear after about two years.

Approximately 50% of women with ASCUS/ASC Pap results are positive for HPV DNA (Solomon et al, 2001). ASC can also be caused by inflammation, atrophy or infection. In the case of ASC-H, 85% of liquid-based cytology and 70% of conventional Pap tests are associated with positive tests for hrHPV. Most women whose Pap tests indicate low-grade or high-grade squamous intraepithelial lesions (LSIL/HSIL) are HPV DNA-positive (89% and 97%, respectively). Many cases of LSIL are caused by low-risk types that never develop into a pre-malignant condition.
A Pap test is an excellent opportunity to discuss vaccination.

**Suggested Discussion:** “What I am looking for is HPV-related disease. There is a vaccine to prevent this that I think you should consider.”

Detailed references for Q11 (6, 75, 93, 94) may be found in *Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version)* available on the GOC corporate website at www.g-o-c.org.

### Q12. Do condoms protect against HPV?

- Among all viruses causing sexually transmittable infections (STIs), HPV is one of the easiest to acquire.
- Consistent condom use provides some protection against HPV as well as other STIs, e.g., gonorrhea, chlamydia, and human immunodeficiency virus (HIV).

Even if condoms are worn during intercourse and worn correctly, there is no guarantee of complete protection against HPV. The reason for this is that HPV transmission requires only skin-to-skin transmission; penetration is not essential. When penetration occurs, digital penetration is sufficient for transmission. In addition, HPV transmission can occur because the condom covers only the penis, leaving the rest of the genitals uncovered. During intercourse, these unprotected areas can come into contact with the vagina, anus, etc.

Studies suggest that condom use does provide protection against HPV transmission; however, protection is not complete. The rate of HPV acquisition in couples who reported using condoms 100% of the time was 70% lower than in women whose partners used condoms less than 5% of the time. Condom use has also been associated with a degree of protection against cervical HSILs and cervical cancer.

Detailed references for Q12 (91, 92, 95–99, 100–107) can be found in *Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version)* available on the GOC corporate website at www.g-o-c.org.
What are the components of the prophylactic vaccines?

- The active ingredients of all three vaccines are virus-like particles (VLPs) that consist entirely of one type of protein (L1), a major component of the viral shell. These are not live viruses.

- The quadrivalent and nonavalent vaccine products do not contain a preservative or antibiotics.

Three prophylactic vaccines have been developed—bivalent, quadrivalent and nonavalent—and are approved for use in Canada. The active ingredients of all three vaccines are VLPs that consist entirely of one type of protein (L1), a major component of the viral shell. None of the vaccines contain viral DNA; they are not live viruses.

**Bivalent vaccine**

Each 0.5 mL dose of the bivalent vaccine contains 20 µg of HPV 16 L1 VLP and 20 µg of HPV 18 L1 VLP. In addition, each dose contains 500 µg aluminum hydroxide and 50 µg 3-deacylated monophosphoryl lipid A. The full composition of the commercial formulation of the bivalent vaccine has not yet been reported. The adjuvant is patented.

**Quadrivalent vaccine**

Each 0.5 mL dose of the quadrivalent vaccine contains the following amounts of L1 protein: approximately 20 µg of HPV 6, 40 µg of HPV 11, 40 µg of HPV 16, and 20 µg of HPV 18. Each 0.5 mL dose also contains approximately 225 µg of aluminum (as amorphous hydroxyphosphate sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 µg of polysorbate 80, and 35 µg of sodium borate as inactive ingredients. The product does not contain a preservative or antibiotics.

**Nonavalent vaccine**

The nonavalent vaccine is a sterile suspension for intramuscular administration. The formulation contains higher amounts of HPV 6, 16, and 18 VLPs than the quadrivalent vaccine and has an adjuvant-to-antigen ratio that is similar to that of the quadrivalent vaccine.
Each 0.5 mL dose contains L1 protein, as follows: approximately 30 mcg of HPV type 6, 40 mcg of HPV type 11, 60 mcg of HPV type 16, 40 mcg of HPV type 18, 20 mcg of HPV type 31, 20 mcg of HPV type 33, 20 mcg of HPV type 45, 20 mcg of HPV type 52, and 20 mcg of HPV type 58.

The adjuvant for the nonavalent vaccine is Merck’s proprietary aluminum-based adjuvant, aluminum hydroxyphosphate sulfate (AAHS), the same adjuvant used in the quadrivalent HPV vaccine and hepatitis B vaccine. Each 0.5 mL dose of the vaccine also contains approximately 500 mcg of aluminum (provided as AAHS), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, and 35 mcg of sodium borate. The product does not contain a preservative or antibiotics.

Detailed references for Q13 (3, 4, 108, 109) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

Who should be vaccinated with HPV prophylactic vaccines?

- The bivalent, quadrivalent and nonavalent vaccines are indicated for all females 9–45 years of age.
- The National Advisory Committee on Immunization (NACI) recommends the bivalent and quadrivalent vaccines for all females aged 9–45 years. NACI has not yet provided recommendations for the nonavalent vaccine.
- The quadrivalent and nonavalent vaccines are indicated for all males aged 9–26 years.
- NACI recommends the quadrivalent vaccine for all males 9–26 years of age AND men who have sex with men regardless of age.

Summary of INDICATIONS and RECOMMENDATIONS for HPV vaccines in Canada:

In Canada, the bivalent vaccine is approved in females aged 9–45 years to prevent cervical cancer and its pre-cursors caused by HPV types 16 and 18. The bivalent vaccine has not been authorized for use in males.

The quadrivalent and nonavalent HPV vaccines are approved for use among females 9–45 years of age for the prevention of cervical, vulvar and vaginal cancers and their pre-cursors; precancerous or dysplastic lesions of the
cervix, vulva and vagina; adenocarcinoma in situ; genital warts; and the quadrivalent vaccine for infections caused by HPV types 6, 11, 16 and 18 and the nonavalent vaccine for infections caused by types 6, 11, 16, 18, 31, 33, 45, 52 and 58. The quadrivalent and nonavalent vaccines are also indicated for males aged 9–45 years for the prevention of genital warts, anal cancer and AIN caused by HPV types 6, 11, 16, and 18 (quadrivalent vaccine) and types 6, 11, 16, 18, 31, 33, 45, 52 and 58 (nonavalent). The bivalent, quadrivalent and nonavalent vaccines have a three-dose regimen. The bivalent vaccine is to be given at months 0, 1, and 6, the quadrivalent and nonavalent at months 0, 2, and 6 months.

**Alternate two-dose schedules for girls 9–13 years of age.** A two-dose schedule is approved for both the bivalent and quadrivalent vaccines. Dosing schedule is 0 and 6 months for the bivalent, with some flexibility (i.e., the second dose should be given between 5 to 7 months after the first dose). The quadrivalent schedule is 0 and 6 months or 0 and 12 months.

**Alternate two-dose schedule for boys 9–13 years of age.** The quadrivalent two-dose schedule for boys is 0 and 6 months or 0 and 12 months.

The nonavalent vaccine is not approved for a two-dose schedule; however, studies are ongoing.

NACI recommends administration of the bivalent vaccine for females 9–26 years of age.

NACI also recommends that the bivalent may be administered to women over 26 years, regardless of previous cervical disease (including cervical cancer) with no defined age limit.

NACI recommends administration of the quadrivalent vaccine for males and females from 9–26 years and for men who have sex with men (MSM). NACI also recommends the quadrivalent vaccine may be administered to women over 26 years, regardless of previous cervical disease (including cervical cancer) with no defined age limit.

NACI has not yet issued recommendations for the nonavalent vaccine.

Detailed references for Q14 (2, 3, 86, 110–117) can be found in *Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version)* available on the GOC corporate website at www.g-o-c.org.
Is there evidence that the vaccines work in the “real world”?

- Yes. We have evidence from numerous jurisdictions of a rapid decline in anogenital warts and high-grade lesions where HPV vaccine programs have been implemented.
- Vaccine effectiveness in these “real world” population-based studies is very similar to the efficacy in the randomized clinical trials.
- In Australia genital warts have virtually disappeared in the vaccine era.

Many reports are now available from Canada, USA, England, Scotland, Germany, Denmark, Sweden and Australia on the effectiveness of HPV vaccination in the real world setting. All reports have demonstrated rapid decreases in the rates of anogenital warts and high-grade lesions.

Ali et al (2013) collected data on anogenital warts in eight sexual health clinics in Australia between 2004 and 2011. Following implementation of a national HPV vaccination program with the quadrivalent vaccine, the incidence of anogenital warts essentially disappeared in those under 21 years of age with a decrease of 92.6%. An important finding from this study was that men who have sex with women also had significant reductions in anogenital warts; however, men who have sex with men saw no reduction. This data reinforces the need for equitable vaccination programs.

The effectiveness of the quadrivalent and bivalent vaccines on cervical abnormalities has also been studied in several countries. The reduction in cervical abnormalities in these studies, including two from Canada with organized programs with the quadrivalent vaccine, mirrored those of the clinical trials, with an approximate reduction of 50% in high-grade lesions. Similar reductions were seen for the bivalent vaccine in an analysis from Scotland, where the bivalent vaccine is the vaccine of choice. Reductions were 50% and 55% for CIN2 and CIN3, respectively. In all studies, as in the clinical trials, effectiveness decreased in older women, due to an increase in prevalent infection with advancing age.

Detailed references for Q15 (118–130, 255, 256, 258) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.
Are HPV vaccines safe and what data are available regarding vaccine side effects or adverse reactions in clinical studies and vaccine programs?

- The bivalent, quadrivalent and nonavalent vaccines are safe and well tolerated.
- HPV vaccines do not contain any living virus.
- More than 170 million doses of the quadrivalent vaccine have been distributed globally (> 4 million in Canada). No serious adverse events (AEs) were associated with the vaccine and there was no greater risk of AEs than with placebo.
- NACI and Health Canada recommend HPV vaccination for women and men who have already had HPV-related diseases. Vaccines are safe, and offer significant protection against diseases related to HPV genotypes to which they have not yet been exposed.
- There is ongoing surveillance by health care authorities, companies, and registries.
- Long-term follow-up studies of bivalent and quadrivalent vaccines confirm their general safety.

The safety and tolerability of bivalent and quadrivalent vaccines have been evaluated in many studies, with similar profiles in the vaccinated and control groups, irrespective of age or ethnicity. Safety studies indicated that local and systemic injection-related symptoms were generally mild. A systematic review and meta-analysis by Lu et al (2011) concluded that prophylactic bivalent and quadrivalent HPV vaccines are safe and well tolerated. Further, they have high efficacy in preventing persistent infections and cervical diseases associated with the HPV types in the respective vaccines.

Long-term follow-up studies of bivalent and quadrivalent vaccines confirm the general safety of each product. In a cohort of Brazilian women aged 15–25 years, vaccine efficacy, immunogenicity and safety were reported for the bivalent vaccine for up to 9.4 years. The quadrivalent has over nine years of data with no identified safety concerns. Early data reported the safety and tolerability of the nonavalent vaccine during clinical trials as reported by Joura et al (2015).
The most common AE reported for all three vaccines in trials and clinical experience were injection site reaction, described as pain, swelling, and erythema of light to moderate intensity in 95% of cases. Systemic symptoms, such as fever, nausea, vomiting, dizziness, myalgia, and diarrhoea were reported.

According to a recent review regarding HPV vaccine safety, serious AEs considered as vaccine-related were rare and very similar to other compulsory, well-known vaccines. Severe AEs, such as persistent headache, hypertension, gastroenteritis, and bronchospasm, were described in no more than 0.5% of cases. To date, there is no evidence that metal allergy, (i.e., to the aluminum adjuvant) has been a significant concern. According to this review by De Vincenzo et al (2014), there have been no reports of increased risk of allergic reaction or autoimmune disorders related to the quadrivalent vaccine; both the bivalent and quadrivalent vaccines reportedly have very strong safety profiles.

Pregnancy outcomes were of special interest given the target age for vaccination. No statistically significant increase in miscarriage rates was reported for either the bivalent or quadrivalent vaccine. HPV vaccination is not recommended for pregnant women, because there is insufficient data to ensure safety of the foetus. Of note: the pregnant women who were recorded and observed in the clinical trials had the same rate of congenital abnormalities as that seen in young women who were not vaccinated.

In December 2013, the WHO’s Global Advisory Committee on Vaccine Safety reviewed reports of serious AEs regarding HPV and other vaccines. They found no evidence regarding elevated risk for autoimmune diseases among vaccine recipients, compared to those who had not received the vaccine. The Committee expressed reassurance of the safety profile of HPV vaccines, and reaffirmed the need for ongoing monitoring and surveillance. In particular they underlined the need for collection and review of high quality data.

Detailed references for Q16 (132–142, 265–267) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

q17 How is the long-term safety profile of HPV prophylactic vaccines monitored?

- Vaccine Adverse Event Reporting System (VAERS) is a post-marketing surveillance system that is available to the general public and to health care professionals to submit and receive information and to report AEs: https://vaers.hhs.gov/index.
The long-term safety, type-specific immunogenicity, duration of efficacy, and pregnancy outcomes among women who first received HPV prophylactic vaccines as part of clinical studies have been, and continue to be, evaluated in Northern Europe using the Nordic registry program.

A pregnancy registry also monitors pregnancy outcomes in women who received quadrivalent HPV vaccine in North America.

Pregnancy Registry for North America (Tel: 1-800-567-2594) or the Vaccine Safety Section at Public Health Agency of Canada (Tel: 1-866-844-0018).

**VAERS**

In the USA, federal agencies and vaccine manufacturers independently conduct vaccine safety monitoring and evaluation after vaccine licensing. From June 2006 until March 2014, approximately 67 million doses of quadrivalent vaccine were distributed in the United States. From October 2009 through March 2014, a total of 719,000 doses of bivalent vaccine were distributed.

Overall, quadrivalent vaccine accounted for approximately 99% of doses distributed since 2006. Multiple studies provided evidence supporting the safety of HPV vaccines. Between June 2006 and March 2014, VAERS received 25,176 reports of AEs after HPV vaccination in the United States. Among these, quadrivalent vaccine was cited in 99% of reports, as it accounts for 99% of the HPV vaccines administered (22,867 and 2,196 reports among females and males, respectively); 92.4% of the quadrivalent vaccine reports were classified as not serious. Overall, reporting AEs to VAERS is consistent with pre-licensure clinical trial data and consistent with the 2009 published summary of the first two and one-half years of post-licensure reporting to VAERS.

**Safety and efficacy registries**

The long-term safety, type-specific immunogenicity, and efficacy of the HPV prophylactic vaccines have been evaluated in Northern Europe (Scandinavian countries and Finland) using the Nordic registry program. For the bivalent vaccine, 4,875 Finnish women were vaccinated in 2004/2005 as part of a four-year phase III clinical trial. They have been followed beyond duration of the trial. For the quadrivalent vaccine, 7,320 women (5,570 from Denmark, Iceland, Norway, and Sweden and 1,750 from Finland) were vaccinated in 2002/2003 as part of the FUTURE II clinical study; they were followed for four years in post-trial surveillance and within regional registries over their lifetimes.

These Nordic countries have unique cervical cancer screening registries that allow for close tracking of cervical cytology and biopsy results, using national identification numbers. Personal identifiers can also be used to link vaccine
recipients to national health registries (e.g., for cancer and other chronic
diseases) to monitor the long-term safety and effectiveness of the vaccines.
Serum samples from vaccine recipients were collected to determine HPV
antibody levels. Vaccine recipients were followed for pregnancy outcomes.

In the PATRICIA end-of-study analysis, serious AEs were considered related
in 10 (0.1%) cases in the vaccine group and five (0.1%) in the control group
(Lehtinen et al (2012)).

**Ongoing phase III clinical trial**

Results from the FUTURE II study (2007) reported ten years’ follow-up of
females aged 15–26 years. There were no new cases of disease related to
HPV 16 and 18 (CIN2 or worse), AIS and cervical cancer; and nine years’
seropositivity was reported.

**Phase IV clinical studies**

Effectiveness of different vaccination strategies (to reduce HPV prevalence in
the population) was evaluated in community-based phase IV clinical studies
in Nordic countries.

A systematic review and meta-analysis by Lu et al (2011) concluded that
prophylactic HPV vaccines are safe, well tolerated and have high efficacy in
preventing persistent infection and cervical diseases associated with the HPV
types in the respective vaccines.

**Pregnancy outcome registries**

In North America, a pregnancy registry will further monitor pregnancy
outcomes in women who received the quadrivalent HPV vaccine. Incidents
can be reported at the following:

Pregnancy Registry for North America (Tel: 1-800-567-2594); or,
Vaccine Safety Section at Public Health Agency of Canada
(Tel: 1-866-844-0018), or;

http://healthycanadians.gc.ca/healthy-living-vie-saine/immunization-
immunisation/coverage-couverture/index-eng.php

The safety profile of the nonavalent vaccine is reportedly acceptable and well
tolerated among females aged 12–26 years who had previously received the
quadrivalent vaccine. Of females 9–26 years of age and males 9–15 years of
age who received the nonavalent vaccine, they rarely discontinued vaccine
use due to adverse experiences. More injection-site reactions were reported
with the nonavalent vaccine, compared to the quadrivalent vaccine, but
reactions were of mild to moderate intensity.
Has there been any HPV genotype replacement since vaccine implementation?

- Type replacement caused by widespread vaccination is theoretically possible, but considered unlikely.
- No type replacement has been reported in four-year follow-up of the bivalent vaccine and six-year follow-up of the quadrivalent vaccine.

**What is type replacement?**

The concept of type replacement refers to a situation in which vaccination, by suppressing the targeted types of pathogens (e.g., viruses), causes related, non-targeted types to become more prevalent or aggressive. Type replacement is a theoretical concern with prophylactic HPV vaccines. However, in the case of HPV, type replacement seems unlikely to occur, since infections with different HPV types appear to be mutually independent.

**Long-term follow-up**

Analyses on type replacement were conducted based on data gathered in phase II and phase III studies. Type replacement has been explored in long-term follow-up studies of vaccinated women in Northern Europe. No type replacement has been reported among older women who were followed for six years after immunization with the quadrivalent vaccine. The possibility of developing diseases caused by a non-vaccine HPV type calls for continued surveillance through cervical screening for all women, regardless of vaccination status.
Will sexually active women benefit from HPV vaccination? Will women treated for previous HPV infection and/or HPV-related cervical or genital diseases benefit from HPV vaccination?

- Yes. According to NACI, women who are sexually active as well as those with HPV-related cervical, anogenital diseases or known HPV infection, will benefit from HPV vaccination.

- The likelihood of exposure to more than one vaccine HPV type is low and even if previously exposed, natural infection does not guarantee protection.

- In large RCTs, both bivalent and quadrivalent vaccines have demonstrated efficacy in preventing diseases related to a vaccine type with which individuals had been previously infected (as measured by seropositivity at baseline).

- Similarly, both vaccines were effective in decreasing or preventing subsequent HPV-related disease among women with previous HPV infection or diseases (CIN or anogenital warts).

- Recent studies of the quadrivalent vaccine suggested that women with prior infection and/or treatment still derived benefit from vaccination, with protection from subsequent diseases.

The likelihood that a woman has been infected with all HPV types targeted by HPV vaccines is very low. In a large study of North American women aged 16–26 years, with up to five lifetime sexual partners, 23% showed signs of current or previous infection. Of these individuals, 6% showed signs of infection with two or more vaccine HPV types; 1.1% with three or more types; and only 0.1% with all four vaccine HPV types. Only 1.0% of women were positive to the two oncogenic types, HPV 16 and 18. Even among women who had cervical dysplasia at baseline, only 8% were positive for both HPV 16 and 18.
Both the bivalent and quadrivalent vaccines have demonstrated efficacy in the following groups:

a) women up to 45 years of age, with no restriction on lifetime partners — greater than 85% reduction;

b) women with evidence of previous infection: in pivotal clinical trials, vaccine recipients had a reduction of up to 100% of disease caused by the same type;

c) women with a history of previous disease: women who were vaccinated and then had cervical surgery were 64.9% less likely to develop CIN2 or worse; and

d) women who received LEEP therapy for CIN2/3 had an approximately 66% reduction in recurrent disease.

Detailed references for Q19 (86, 133, 135, 136, 147–151) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

Q20 Should I recommend the vaccine to males? Why are boys not included in most provincial HPV vaccination programs?

- Yes, the vaccine is recommended for males.
- Men are at risk for several HPV-related cancers and anogenital warts.
- MSM do not benefit from female-only vaccination.
- Among MSM, the risk of anal cancer is the same as that of cervical cancer among women prior to widespread use of Pap tests.
- In 2015, NACI recommended use of the nonavalent vaccine for males 9–26 years of age, as well as for all men who have sex with men (MSM), regardless of age.
- Some provinces are not vaccinating boys; this decision is largely based on current concerns about cost-effectiveness. (See Q21)
- The bivalent vaccine has not been approved for males in Canada.

Because a province has not implemented a publicly funded vaccine program for males does not imply a lack of importance. Men are at risk for several
HPV-related cancers and anogenital warts. Nova Scotia, Prince Edward Island, Manitoba and Alberta have included boys in their school-based HPV vaccine programs.

See Q1, Q5, Q6, Q15, Q28 and Q49.

In the past, HPV was primarily perceived as a disease of the cervix. More recently, epidemiologic data from around the world has further elucidated the burden. This data has clearly defined the burden in men, including the role of HPV in anal and penile cancer. Furthermore, a key finding of the growing attribution of HPV in oropharyngeal cancers, (now defined as an epidemic), has led to re-evaluation of the possible benefits of government-funded universal vaccination programs.

Issues of consideration include, but are not limited to, ethical allocation of medicine, herd effect, burden of disease and vaccine efficacy. Many believe that males should have the same opportunity as females to protect themselves against HPV-related cancers. In addition, although some males will benefit from herd effect, many will not. In particular, MSM are likely to receive no benefit at all and rates of anal cancer in MSM are thought to be as high as cervical cancer rates prior to population-based screening.

Cost is also an issue and several cost-effectiveness studies have been completed.

See Q21.

Detailed references for Q20 (64, 65, 73, 152–154, 259) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

Q21 Is the inclusion of males in an HPV immunization program cost-effective? When will HPV vaccine be funded for boys? Should male partners be vaccinated?

- Most evaluations of cost-effectiveness are based on prevention of cervical cancer and thus, to date, the results vary with respect to male vaccination.
- A recent Ontario study concluded that publicly funded HPV vaccination programs for males could be very cost-effective. The study found that vaccinating 12-year-old boys in Canada in 2012
could save the Canadian health care system between CDN $8 million to $28 million in the cost of caring for HPV-related diseases during this cohort’s lifetime. Vaccinating MSM and males in areas where vaccine uptake in females is less than 70% is reportedly cost-effective.

- Yes, male partners should be vaccinated as per NACI recommendations.

A gender-neutral HPV vaccine program would underscore the need for both genders to share equal responsibility for sexual and reproductive matters. Since 2013, Prince Edward Island, Nova Scotia, Manitoba and Alberta have included boys in the public immunization program.

In modelling studies, there is conflicting evidence as to the cost-effectiveness of vaccinating males. Kim and Goldie (2009) predicted in their USA model that including boys in a vaccine program would not be cost-effective, if vaccine coverage among females was at least 75% and the vaccine provided complete, lifelong efficacy against HPV 16 and 18 cervical diseases. When immunization coverage was assumed to be lower than 50% among girls, Brisson and Drolet’s model (2012) predicted that immunizing boys was cost-effective.

Conclusions from modeling studies have varied due to different input measurements, e.g., few have included the full costs associated with oropharyngeal cancers and the full burden of disease. Previous reports indicated that universal vaccination for MSM is cost-effective even when vaccinating those 20–26 years of age with prior exposure to HPV vaccine types. Also, funded HPV vaccination programs for boys, in areas where uptake has been less than 70% in girls, were considered cost-effective. A recent analysis from Ontario incorporated updated incidence rates of oropharyngeal cancer and the costs associated with treatment. That study found that publicly funded HPV vaccination for boys was very cost-effective even when the uptake in girls is 70%. Vaccinating 12-year-old boys in Canada in 2012 potentially could save the health care system between CDN $8 and $28 million for this theoretical cohort over their lifetime.

Detailed references for Q21 (48, 154, 155, 156, 259) can be found in *Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version)* available on the GOC corporate website at www.g-o-c.org.
I hear that a new nonavalent vaccine is now available. What are the advantages and disadvantages?

- The new nonavalent HPV vaccine had been well studied in females and males and offers a broader range of protection with the addition of five oncogenic HPV types.

- Adding HPV 31, 33, 45, 52 and 58 to existing vaccine types could prevent almost 90% of invasive cervical cancer worldwide.

- There is no evidence of any significant disadvantages; however, the frequency of injection-site AEs was higher with the nonavalent vaccine.

The nonavalent vaccine demonstrated prevention of infection and diseases related to five additional oncogenic HPV types in a susceptible population. The rate of high-grade cervical, vulvar, or vaginal diseases related to HPV 31, 33, 45, 52 and 58 was 0.1 per 1,000 person-years in the nonavalent HPV group, and 1.6 per 1,000 person-years in the quadrivalent HPV group (efficacy of the nonavalent vaccine, 96.7% [95% CI, 80.9 to 99.8]). The nonavalent HPV vaccine did not prevent infection and diseases related to HPV beyond the nine types covered by the vaccine.

The nonavalent HPV vaccine also generated an antibody response to HPV types 6, 11, 16 and 18 that was non-inferior to that generated by the quadrivalent vaccine. Disease incidence related to HPV types 6, 11, 16 and 18 was similar in the two vaccine groups. Therefore, it can be inferred that efficacy of the nonavalent vaccine against diseases related to HPV types 6, 11, 16 and 18 is similar to that of the quadrivalent vaccine.

The nonavalent vaccine was also shown to reduce the incidence of Pap test abnormalities, plus cervical and external genital procedures, i.e., biopsies related to HPV types 31, 33, 45, 52, and 58, by 96.9% (95% CI, 93.6 to 98.6); and cervical definitive therapy procedures by 87.5% (95% CI, 65.7 to 96.0).

The rate of clinical AEs was generally similar in the two vaccine groups (quadrivalent vs. nonavalent). However, AEs related to the injection site was higher in the nonavalent HPV group than in the quadrivalent HPV group (90.7% vs. 84.9%). This result was anticipated, since amounts of the HPV virus-like particle antigens and AAHS adjuvant are higher in the nonavalent HPV
vaccine than in the quadrivalent HPV vaccine. Most injection site AEs were mild or moderate in intensity. Few participants discontinued vaccination during the study because of a vaccine-related AE.

Detailed references for Q22 (4, 30, 139) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

**Q23**

What about the two-dose vaccination program? Is it sufficient and safe?

Why has there been a two-dose vaccine program in Quebec and why are there differences across provinces and territories?

- Recent studies support a two-dose vaccine schedule in younger females 9–14 years of age.
- In December 2014, the World Health Organization recommended a two-dose approach for HPV vaccine.
- NACI made recommendations in 2014.
- Quebec and British Columbia have always implemented a two-dose program for the school-based pre-adolescent vaccine program, including a third dose if needed.
- Other provinces are adopting the two-dose programs for school-based programs.

“NACI now recommends that (bivalent and quadrivalent) vaccines may be administered to immunocompetent individuals 9 to 14 years of age as two separate doses at month 0 and the second from 6 to 12 months later. Immuno-compromised and immune-competent HIV-infected individuals, and individuals who have not received any dose of HPV vaccine by 15 years of age, should continue to receive three doses of HPV vaccine.

A two-dose HPV immunization schedule among immunocompetent 9 to 14 year olds is expected to provide similar protective efficacy compared to a three-dose schedule in immunocompetent individuals aged 9 to 26 years. This revised schedule of administration and may allow for potential cost savings plus other individual and programmatic advantages.”
When the federal government first approved HPV vaccines in Canada, each province and territory decided when, where, how and for whom the vaccines would be available. Consequently, different strategies were implemented across provinces and territories regarding targeted age groups, program delivery and dose schedule(s). Since initial implementation, many studies have documented experience across the country.

Several studies, including a Canadian immunogenicity trial by Dobson et al (2013), supported a two-dose HPV vaccine schedule. These studies have shown that for pre-adolescents 9–13 or 14 years of age, antibody titres on a two-dose regimen are non-inferior to those achieved with a three-dose regimen in older girls and young women (in whom efficacy has been demonstrated). Romanowski et al (2011) and Lazcano-Ponce et al (2014) reported similar outcomes of non-inferiority with a two-dose regimen, compared to three doses.

Quebec data showed that the first dose of HPV vaccine ensured priming in 9–10 year-old girls and that the second dose, given six months later, induced an anamnestic response. Geometric mean antibody titers (GMTs) increased 55- to 100-fold. Three years later, there was 99% to 100% persistence of antibodies and an excellent immune memory (at month 42 of the study) after a third challenge dose. Antibodies were slightly higher one month after the third dose, compared to one month after the second dose. HPV vaccines administered to girls aged 9–11 years have been well tolerated. However, a two-dose schedule would likely generate fewer adverse events following immunization (AEFI) than a three-dose schedule.

Based on this body of evidence, a variety of expert immunization advisory committees have now recommended a two-dose schedule. This includes the World Health Organization’s Strategic Advisory Group of Experts on Immunization, the Swiss Federal Public Health Office, the United Kingdom’s Joint Committee on Vaccination and Immunisation, and the European Medicines Agency. In December 2014, the WHO released their updated position paper on HPV vaccines, in which they recommended a two-dose schedule for both bivalent and quadrivalent HPV vaccines. The schedule would include two doses separated by six months for females younger than 15 years and before sexual activity. A regular three-dose schedule was still recommended for females fifteen years and older, as well as for those who are immune-compromised and/or HIV-infected.

In Canada, NACI recently recommended a two-dose vaccine schedule. Both Quebec and British Columbia are now using a two-dose program for their school-based pre-adolescent vaccine programs. So far, published data relate to immunological outcomes. No data is publicly available from randomized controlled trials about the clinical efficacy of two-dose schedules in adolescents.
Detailed references for Q23 (157–165, 167–171) can be found in *Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version)* available on the GOC corporate website at www.g-o-c.org.

**Q24** What is the benefit of vaccinating women over the age of 26 years and what studies have been done in this age group?

- Women over 26 years benefit from HPV vaccination.
- The bivalent, quadrivalent and nonavalent vaccines are all indicated for women up to 45 years of age.
- Risk of HPV acquisition does not correlate with age; therefore, women in their 30s and 40s, with new sexual partners are just as likely as their younger counterparts to acquire HPV.

Sexually active mid-adult women have the same risk of HPV acquisition as younger women. Winer et al (2012) conducted a study in women 25–65 years of age who participated in online dating. In this study, HPV acquisition did not correlate with age, but rather with sexual activity. Therefore if mid-adult women are in a new relationship or planning on new partners, they are at risk for HPV acquisition.

In vaccine trials, the percentage of women who were positive for all vaccine HPV types at baseline was very low. For example, in the study of the quadrivalent vaccine, only 0.1% of women 26–45 years of age were positive for all four types. Therefore, patients will derive benefit from preventing types to which they have not been exposed. In addition, vaccination has been shown to prevent new infection and diseases, including infection and disease caused by a type previously acquired by the individual.

The bivalent and quadrivalent prophylactic HPV vaccines have been evaluated in well-designed studies among women over the age of 26 years. In the end-of-study follow-up of the quadrivalent vaccine, high efficacy, immunogenicity and safety of the vaccine were demonstrated for up to six years. High rates of seropositivity were reported among vaccine recipients at the end of the study (HPV 6 [91.5%], 11 [92.0%], 16 [97.4%], and 18 [47.9%]), in spite of prior exposure to HPV in this age group. Efficacy against the combined end-point of persistent infection, CIN, or external genital lesions was 88.7% in the per-protocol population and 47.2% in the intention-to-
treat arm, indicating good protection for women, with and without previous exposure. Skinner et al (2014) followed those women in the age range from over 26 to > 46 years who received the bivalent vaccine. They reported vaccine efficacy against HPV 16 and 18-related six-month persistent infection, or CIN1+, with significant protection in all age groups combined (81.1% and 97.7% respectively; CI 52.1-94.1), in the 26–35 years age group (83.5%, 45.0–96.8), and in the 36–45 years age group (77.2%, 2.8–96.9).

Detailed references for Q24 (2, 86, 133, 135, 136, 172, 173, 174, 260) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

Q25 Should health care providers be vaccinated?

- Health care personnel are at potential risk from airborne contaminants from both laser and electrocautery procedures.
- Health care providers need to assess individual risk in both their personal and professional lives to decide if HPV vaccination is right for them.

Concerns have been raised in certain colposcopy clinics about the potential impact for treating clinicians as to airborne transmission of HPV on oropharyngeal and dermal infections. A recent case report highlighted two gynecologists with extensive laser use who subsequently developed HPV-positive tonsillar cancers.

Among other contaminants, E coli, staphylococcus, HPV, HIV and hepatitis B virus have reportedly been detected in plume, whether generated by laser or by electrocautery. Bargman (2011) indicated that an increased risk of warts in laser operators has been reported, as has one case of laryngeal papillomas in a laser surgeon. Laser operators and other health care personnel are at potential risk from airborne contaminants; laser safety officers and operators are responsible for ensuring that recommended ventilation equipment is in place. A recent Canadian study by Brace et al (2014) showed that cautery was capable of creating more ultrafine particles than laser, concluding that use of appropriate N95 masks should be considered. Authors noted that the air circulation in an operating room with HEPA filtration was such that air quality was excellent; however, most cervical treatments are performed in a clinic with minimal filtration or circulation.
When treating patients with HPV-related diseases, clinicians need to be conscientious about adhering to appropriate medical techniques, including washing hands, wearing gloves, and using sterile equipment, masks, eye protection, etc., depending on the procedure.

Clinicians need to consider vaccination based on recommendations for the general public. The comments offered here are based on clinician consensus; there are no data related to this particular issue.

Detailed references for Q25 (175–177) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

How long does protection last with HPV prophylactic vaccines?

- Current data show protection for up to nine and one-third years for the bivalent vaccine and more than eight years for the quadrivalent vaccine as of 2015.

- Long-term protection from diseases will be determined from data collected during ongoing long-term clinical trials, population-based immunization programs and cancer registry data.

- Indirect evidence based on immunological studies suggests durable protection.

**Published clinical trial data**

The long-term efficacy of HPV vaccines is a key factor in determining how vaccines should be used and how their benefits will compare to their costs. The primary target group for vaccination is HPV-naive pre-adolescents, for whom the highest risk of HPV infection may lie eight to ten years in the future. Longer duration of protection is the best outcome.

**Bivalent HPV vaccine**

In the phase III efficacy trial, women aged 15–26 years were followed for a median of 47 months after the first vaccine dose. The longest follow-up from the bivalent vaccine clinical trials was from the phase II trial; a subset of participants were followed for up to nine and one-third years after the first dose. Among the 437 participants evaluated, efficacy for prevention of one-year persistent infection with HPV 16 and 18 was 100% (95% CI: 61.4–100).
Further follow-up data on duration of protection will be available from female participants in the phase III trial. Adolescents who were vaccinated from 10–15 years of age in an immunogenicity trial will be followed as they become sexually active.

In women older than 25 years, the bivalent vaccine was reportedly efficacious against infections and cervical abnormalities associated with the vaccine types; the mean follow-up time was 40.3 months.

**Quadrivalent HPV vaccine**

As reported in the August 2014 recommendations from the Advisory Committee on Immunization Practices (ACIP), women aged 16–26 years were followed in phase III trials, for a mean of 42 months after the first dose. The longest follow-up for the quadrivalent vaccine was from the phase II trial (protocol 007); a subset of participants (n = 241) was followed for 60 months after dose one. Efficacy against vaccine-type persistent infection or disease was 95.8% (95% CI, 83.8–99.5) and efficacy against vaccine type-related CIN or external genital lesions was 100% (95% CI, 12.4–100). Additional data on duration of protection will be available from a follow-up of approximately 5,500 Nordic girls and women enrolled in one of the phase III quadrivalent trials. This sample will be followed for at least 10 to 14 years after vaccination; serologic testing will be conducted nine and fourteen years after vaccination among original vaccine recipients. Pap test results will be linked to pathology specimens for sectioning and HPV DNA testing by PCR. Follow-up data from seven to eight years showed no evidence of waning protection.

Boys and men in the phase III trial will be followed for 10 years after vaccination. Adolescent girls and boys who were vaccinated from 10–15 years of age in an immunogenicity study will also be followed as they become sexually active. Through eight years of follow-up, no cases of disease were observed in girls or women, or infection in boys or men, related to HPV types 6, 11, 16, or 18.

In a follow-up of clinical trials of the quadrivalent vaccine, women 24–45 years of age, with current or previous infection with HPV, were protected against HPV types targeted by the vaccine for up to six years, as reported by Luna et al (2013).

**Nonavalent HPV vaccine**

Efficacy of the nonavalent HPV vaccine was assessed in an active comparator-controlled, double-blind, randomized clinical study that included 14,204 women 16–26 years of age. Subjects were enrolled and vaccinated without pre-screening for active HPV infection. Participants were followed for a median duration of 40 months (range 0–64 months) after the last vaccination dose.
Detailed references for Q26 (4, 40, 136, 139, 178–184) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

q27 Will a vaccine booster be necessary?

- It is not yet known whether a booster will be needed.
- Current information on immune system response to the vaccine suggests that protection may be long lasting.
- Close follow-up of women who were vaccinated during clinical trials will continue for at least 10 years and provide the information required to determine need for a booster.

At this time, we do not know if a booster dose will be needed. Data indicate that antibody levels fell from a maximum following immunization to levels comparable to, or higher than, those seen in natural infection. These levels persisted for at least eight years or more after vaccination. Published data on disease protection, i.e., the number of cases of HPV types prevented by the vaccine, is available for up to nine and one-third years for the bivalent (Naud et al 2014) and more than eight years for the quadrivalent vaccine (Ferris et al 2014). Close follow-up of women participating in the efficacy trials will continue for at least 10 years after initial vaccination and provide the information required to determine need for a booster.

See also Q8

Detailed references for Q27 (134, 181, 183, 185, 186) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

q28 Will HPV vaccines protect against non-gynecological cancers? For example, do HPV vaccines protect against oropharyngeal and anal diseases related to HPV?

- Yes, HPV vaccines do protect against a proportion of non-gynecological precancerous lesions and pre-invasive diseases.
Expert opinion suggests that they will likely prevent cancer, but evidence is still emerging with respect to non-gynecological diseases.

The bivalent and quadrivalent vaccines have been shown to decrease HPV-related oropharyngeal infection.

The quadrivalent and nonavalent vaccines are indicated for the prevention of anal cancer and expert opinion suggests that the bivalent vaccine would also be highly effective.

Anal and oropharyngeal cancers (OPCs) are increasing in men and women, mostly due to changes in sexual behaviour.

The quadrivalent is the only vaccine to demonstrate effectiveness in reducing HPV-related anal disease in a controlled study. Palefsky et al (2011) assigned healthy young (16–26 years) MSM (n = 602) to either a placebo group or a group that received the quadrivalent vaccine. The primary efficacy objective was the prevention of AIN or anal cancer (related to HPV types 6, 11, 16 and 18). Incidence of AIN2/3 (HPV types 6, 11, 16 and 18) was lowered by 54.2% (95% CI: 18.0–75.3) in the intent-to-treat population and by 74.9% (95% CI: 8.8–95.4) in the per-protocol efficacy population. No serious AEs related to the vaccine were identified. The quadrivalent and nonavalent vaccines are indicated for the prevention of anal cancer and AIN. As most anal cancers are associated with HPV 16 and 18, expert opinion suggests that the bivalent vaccine would also be highly effective.

The bivalent vaccine demonstrated a significant reduction in oral infection in a study of 7,466 women. In this four-year blinded study, the primary analysis assessed prevalent oral HPV infection. Women aged 18–25 years were randomized (1:1) to receive either HPV 16 and 18 vaccine or hepatitis A vaccine as control. Participants (N = 5,840) provided oral specimens to evaluate vaccine efficacy (VE) against oral infections. Four years after vaccination there were fifteen HPV 16 and 18 infections in the control group versus only one in the vaccine group, representing a 93.3% reduction in oral infection. As with anal cancer, most OPCs (> 90%) are associated with HPV types 16 and 18. Expert opinion suggests that all three vaccines will be highly effective in preventing OPC.

Q29
How many doses of nonavalent vaccine will be required? What is the recommended schedule?

- The schedule for the nonavalent vaccine is three doses given at 0, 2, and 6 months.

Although the bivalent and quadrivalent vaccines both have a three-dose schedule, an alternate two-dose schedule for boys and girls aged 9–14 is an option. However, data for a two-dose schedule is not available for the nonavalent vaccine.

See reference for Q29 (4) in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

Q30
Why is the uptake of HPV vaccination poor in some jurisdictions and good in others?

- Many factors can influence vaccine acceptability and uptake.
- Vaccine effectiveness, safety and knowledge, as well as recommendations from clinicians and parents, are important factors that influence vaccine acceptability.
- Primary care providers and parents play an important role in promoting vaccines.
- Accurate evidence-based knowledge and information are critical.
- Public education initiatives are important so that target groups understand the basis for a vaccine program.

Many factors influence vaccine uptake including timing of the decision, sufficient time for scaling up resources to meet the demand, and resource capacity within public health. Critical factors for acceptability include a well-informed general public and medical community. If knowledge of the subject
is limited, support for a vaccine will likely be cautious. In Canada, acceptability and subsequent uptake of the initial HPV vaccine program in schools varied widely across the country.

The most important factors related to vaccine acceptability are vaccine effectiveness, safety, public knowledge and recommendations from clinicians and parents. Accurate knowledge of HPV and associated disease(s) was limited in both public and medical communities when the vaccines were originally approved. However, knowledge of HPV-associated diseases and the benefits of vaccination have increased over the past few years, and uptake has improved to approximately 70% in school-based programs.

In addition, for the private market (patients paying out-of-pocket or through private insurance), a better understanding of the burden of the disease in men and mid-adult women, and the benefits of vaccination for each group, has led to greater patient and physician acceptance and uptake in these groups.

As a clinician, how can I support vaccine uptake?

- Stay up-to-date with the evidence.
- Promote HPV vaccines with the intended target groups.
- Remember the importance of your role in influencing patient behaviour.
- If you are going to recommend vaccination, provide a strong recommendation.

Detailed references for Q30 (188–199) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

q31 With the availability of the new nonavalent HPV vaccine, should I defer recommending HPV vaccination until it is clinically available?

- No—do not delay recommending the vaccine.

The nonavalent vaccine was approved for use in Canada in February 2015 and is readily available across Canada.
How do you complete immunization if the recommended schedule is interrupted? If a patient delays the third vaccine dose, how long is too long?

- Do not start again; continue with the subsequent doses according to manufacturer’s directions.

NACI recommends that if the vaccine schedule is interrupted for any of the vaccines, there is no need to restart it. If the series is interrupted after the first dose, give the second dose as soon as possible. If only the third dose is delayed, administer that as soon as possible. Among recipients 9–14 years of age, a two-dose administration is satisfactory, i.e., if the second dose is missed, administering at six months would complete the vaccination.

The nonavalent product monograph suggests contacting a physician if a dose is missed. It also refers people to their local Public Health Unit to take advantage of their vaccine expertise and recommendations.

Detailed references for Q32 (2, 4, 200) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

Does the vaccine have to be refrigerated if not used immediately?

- No, there is a window of up to a total of 72 hours when the vaccine can be out of refrigeration.

- However, HPV vaccines generally require a cold chain, so refrigerated storage is necessary to comply with what is recommended.

Refrigerated storage is necessary to follow recommended procedures to maintain the required cold chain for HPV vaccines. All three vaccines should be stored between 2°C and 8°C and discarded if they become frozen or discoloured.
All three vaccines can be administered, provided total (cumulative multiple excursion) time out of refrigeration (at temperatures between 8°C and 25°C) does not exceed 72 hours. Cumulative multiple excursions between 0°C and 2°C are also permitted as long as the total time between 0°C and 2°C does not exceed 72 hours.

Detailed references for Q33 (3–5, 201) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

Q34

When the new nonavalent vaccine is available, should women who received the quadrivalent vaccine receive a booster with the nonavalent vaccine?

- There is no evidence to support a booster with the nonavalent vaccine.
- Women may choose to receive the nonavalent vaccine because of the possible added benefit.
- Efficacy of both vaccines is strong, at levels significantly higher than natural immunity.

At this point there is no evidence to support boosters or further single-dose administration of any HPV vaccine. There is no known additional benefit.

In a study by Luxembourg et al (2014), the experimental group (girls and women aged 12–26 years) received three doses of the nonavalent vaccine after having received the quadrivalent vaccine. To date, there is no evidence that receiving both vaccines is necessary. Data suggested that administration of a three-dose regimen of nonavalent HPV vaccine to these girls and young women was:

a) highly immunogenic, and resulted in the development of acceptable seropositivity rates to HPV types 31, 33, 45, 52, 58; and,

b) generally well tolerated with an acceptable overall safety profile.
Completion of a vaccine series with the nonavalent HPV vaccine in people who started a series with the quadrivalent HPV vaccine has not been assessed in clinical studies. Advisory committees such as NACI, ACIP, and others around the world will likely provide guidance to health care providers on this topic.

Detailed references for Q34 (2, 138) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

Q35 What are the contraindications to HPV vaccination?

- HPV vaccines are not appropriate for people who are hypersensitive to any component of the vaccines.
- Patients who develop symptoms indicative of hypersensitivity after receiving a dose of any HPV vaccine should not receive additional doses.
- People with anaphylactic latex allergy should not receive the bivalent vaccine (Cervarix®) because doses are provided in pre-filled syringes that contain latex.

**Quadrivalent and nonavalent vaccines should not be administered to:**

a) those who are hypersensitive to either Gardasil® or Gardasil®9 or to any ingredient in the formulation or component of the container (for a complete listing, see the dosage forms, composition, and packaging section of the product monograph); or

b) individuals who develop symptoms indicative of hypersensitivity after receiving a dose of Gardasil®9 or Gardasil®. These individuals should not receive further doses of Gardasil®9.

**Bivalent vaccine should not be administered to:**

- Girls or women with a known hypersensitivity to any component in the vaccine (for a complete listing, see the dosage forms, composition and packaging sections of the product monograph).

Detailed references for Q35 (3–5) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.
Should pregnant or lactating women be vaccinated with HPV prophylactic vaccines? How soon after giving birth can a mother be vaccinated?

- HPV vaccines are not recommended during pregnancy.
- If a woman has already started a three-dose vaccine regimen, administration of the remaining dose(s) can be deferred until after delivery.
- A woman can be vaccinated immediately after giving birth.
- Lactating women may be vaccinated.

HPV prophylactic vaccines are not recommended for administration during pregnancy. During clinical studies of the quadrivalent HPV vaccine among women who reported pregnancy before completing the three-dose vaccination regimen, administration of the remaining vaccine doses was deferred until after the pregnancy.

During clinical trials of the quadrivalent vaccine, 944 women who received the vaccine and 957 of those who received placebo became pregnant. The proportion of pregnancies with an adverse outcome were comparable in the vaccine and placebo groups. Overall, 4.2% of vaccine and 4.3% of placebo recipients who reported a pregnancy experienced a serious AE. The types of congenital anomalies were consistent with data from population-based birth registries.

The bivalent vaccine is not recommended for pregnant women or for those who are considering pregnancy within two months of the first dose. The genotoxicity and reproductive toxicity of monophosphoryl lipid A, a component of the bivalent vaccine adjuvant, have been assessed via in vitro assays and animal studies. While no abnormal effects have been demonstrated, vaccination just prior to or during pregnancy is not recommended.

**Pregnancy outcome registries**

In North America, a pregnancy registry will further monitor pregnancy outcomes in women who received the quadrivalent HPV vaccine.
Can a HPV vaccine be given while breast-feeding?

NACI did not make recommendations about immunization of women who breastfeed because they found no relevant data. Most major authorities, including CDC and PHAC, have approved vaccination of women during lactation.

Detailed references for Q36 (2, 3–5, 157, 179) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

Q37 Can HPV prophylactic vaccines be given concomitantly with other vaccines?

- Yes. Bivalent, quadrivalent and nonavalent vaccines can be administered at the same time as the recombinant hepatitis B vaccine and other age-appropriate vaccines, such as tetanus/diphtheria/pertussis (Tdap) and meningococcal conjugate vaccines.

Results from clinical studies indicate that the quadrivalent vaccine may be administered at the same time (at a separate injection site) as the recombinant hepatitis B vaccine. Immune responses to both vaccines were similar whether they were administered at the same or separate visits. Also the frequency of AEs observed with concomitant administration was similar to the frequency when the quadrivalent vaccine was given alone. Kosalaraksa et al (2014) also indicated that there was no interference with the immune response when nonavalent HPV vaccine and REPEVAX (a diphtheria, pertussis, tetanus, polio (DPTP) vaccine) were administered concomitantly.

According to the NACI guidelines and based on their review of relevant studies of the first two HPV vaccines, either the bivalent or quadrivalent vaccine can be administered at the same visit as other age-appropriate vaccines. Other vaccines might include the Tdap, hepatitis B or
meningococcal conjugate vaccines. HPV vaccines are not live vaccines and are free of components that may diminish the efficacy or safety of other vaccines. Such an approach is likely to increase adherence to the recommended vaccine schedule.

This recommendation is in agreement with the general guideline that most commonly used vaccines can be safely administered at the same time, with the exception of some live parenteral vaccines. Preliminary data regarding this aspect of the nonavalent vaccine was presented at the IPV Conference in 2014, with similar results to those of the bi- and quadrivalent vaccines.

Detailed references for Q37 (2, 3, 202, 203) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

**Q38** Can HPV prophylactic vaccines cause HPV-related diseases in immunized or immunocompromised individuals?

- No. The vaccines consist of VLPs that contain no viral DNA and cannot infect cells or reproduce.
- Immunocompromised individuals can receive the bivalent or quadrivalent vaccine; however, the immune response might be weaker than in immunocompetent persons.
- Transplant patients should be vaccinated prior to transplant.

HPV prophylactic vaccines contain VLPs, empty shells consisting of viral protein that closely simulate HPV, and are capable of generating an immune response. Because VLPs contain no viral DNA, they cannot infect cells or reproduce.

Immunocompromised patients can receive the quadrivalent vaccine; however, their immune response might be weaker than in immunocompetent persons. Because they are not live vaccines, any of the bivalent, quadrivalent or nonavalent vaccines can be administered to patients who are immunocompromised as a result of disease or medications. Because the bivalent vaccine is not indicated for males, only the quadrivalent and nonavalent vaccine would be administered to immunocompromised males. Nevertheless, the immunogenicity and efficacy of these vaccines have not
been fully determined in this general immunosuppressed population, so individuals may not benefit from these vaccines (NACI Recommendation Grade I). Further study is required.

Clinician consensus opinion is that transplant patients should be vaccinated prior to transplant because of the higher prevalence of HPV-related disease incidence and severity after transplant.

Detailed references for Q38 (49, 137–140, 179, 181, 204–208) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

**Q39**

Will prophylactic HPV vaccines help treat established current HPV infection or slow the progression to cancer pre-cursors?

- HPV vaccines are intended for prevention, not treatment, of HPV-related diseases.
- However, women who are infected with one HPV type will derive future protection against this and other types targeted by the vaccine.
- In clinical trials, among females who had vaccine-type HPV DNA detected at study enrolment (either seropositive or seronegative), there was no efficacy against progression to disease or impact on clearance of infection of that HPV type.

Current HPV vaccines are intended for prevention, not treatment, of HPV-related diseases. If a patient has active disease (HPV DNA positive) the HPV vaccines will not provide benefit for that individual lesion. However patients will receive protection from new lesions caused by all types included in the vaccine, including the type in the original lesion.

Joura et al (2012) reported the efficacy of HPV vaccines in preventing new CIN2+ in women who had previously been treated for HPV-related cervical abnormalities. Kang et al (2013) reported that immunization with the quadrivalent vaccine after LEEP may prevent a recurrence of CIN2/3. Also, a study by Swedish et al (2012) found that vaccination provided significant reductions in new lesions or recurrence among men with high-grade AIN.
who were treated and then vaccinated. Additional research is required to determine whether vaccination may help treat established infections or to slow the progression of cervical disease.

Efforts to develop a vaccine for the treatment of HPV infections, cervical lesions and cervical cancer are ongoing, but so far none have reached the stage of approval.

Detailed references for Q39 (3, 48, 147, 148, 181, 183, 209–220) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

How do bivalent, quadrivalent and new nonavalent HPV vaccines differ?

- The bivalent HPV vaccine targets HPV types 16 and 18, responsible for approximately 70% of cervical cancers.

- The quadrivalent vaccine also targets HPV 16 and 18; in addition, it targets HPV types 6 and 11 (non-oncogenic), which are responsible for most (~90%) cases of genital warts.

- The nonavalent vaccine targets the same four HPV types as the quadrivalent vaccine, plus HPV types 31, 33, 45, 52, and 58 that account for about 20% of additional cervical cancers, a total of about 90% of cervical cancers, and 90% of genital warts.

- All three vaccines consist of VLPs, empty virus shells that contain no DNA; however, VLP production methods differ among the bivalent, quadrivalent and nonavalent vaccines.

Table 4 in the comprehensive version of this document compares the main characteristics of the bivalent, quadrivalent and nonavalent HPV vaccines.

All three HPV vaccines are available in Canada. They are similar in many ways; however, there are some differences. All three vaccines consist of VLPs, which are empty virus shells containing no HPV DNA. The bivalent HPV vaccine targets HPV types 16 and 18, responsible for approximately 70% of cervical cancer. The quadrivalent vaccine also targets HPV 16 and 18, as well as HPV 6 and 11, offering protection against 70% of cervical cancers and 90% of genital wart cases. The nonavalent offers additional protection against HPV types 31, 33, 45, 52, and 58, thereby improving protection against 90% of cervical
cancers and 90% of genital wart cases. The additional types in the nonavalent vaccine also offer additional protection for other HPV-related cancers such as vulvar and anal cancer.

The bivalent vaccine is produced in baculovirus; quadrivalent and nonavalent vaccines are produced in yeast (Saccharomyces cerevisiae). The vaccines contain different adjuvants: the bivalent vaccine contains a novel ASO4 adjuvant, while the quadrivalent and nonavalent vaccines contain a proprietary aluminum adjuvant. The schedule for administration of the three vaccines differ slightly.

See Q14 and Q29 for dosing information.

The vaccines also have different indications in Canada, with the main difference being that the quadrivalent and nonavalent vaccines are indicated in males and the bivalent vaccine is not.

Detailed references for Q40 (3–5, 109, 139) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

Q41 Does a patient have protection if only part of the recommended vaccination protocol is completed?

- There is evidence that two doses of either the bivalent or quadrivalent vaccine may provide adequate protection.
- There is strong evidence to support a two-dose schedule for HPV bivalent and quadrivalent vaccines in young girls and boys.

See also Q23 and Q32 for details and recommendations for the two-dose schedule for young girls.

Based on outcomes of a randomized study, Romanowski et al (2011) concluded that two doses of the bivalent vaccine were likely adequate, with equivalent immune responses found in younger women (aged 15–25 years) after two and four years of follow-up. Similarly, Kreimer et al (2011) reported that two doses of the bivalent vaccine were as protective as three doses for women aged 18–25 years.
Lin et al (2014) reported non-inferiority of two doses of quadrivalent vaccine in college-age males (18–25 years). In all these studies, vaccine doses had to be given at least six months apart.

NACI offers a recommendation for a two-dose schedule for the bivalent and quadrivalent vaccines. Studies are underway for the nonavalent vaccine.

Detailed references for Q41 (161, 163, 221, 222) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

Will HPV vaccines protect against other HPV types, i.e., will they offer cross-protection? What is cross-protection?

Cross-protection is defined as protection against infection or disease that extends beyond the HPV types targeted by the vaccine.

There is evidence of cross-protection with the bivalent vaccine against infection with HPV types 31, 33, 45, and 51 and CIN2+.

The quadrivalent vaccine reportedly protects against infection with HPV types 31, 33, 45, 52, and 58.

The end-of-study analysis of the PATRICIA trial of the bivalent vaccine assessed cross-protection of oncogenic HPV types that were not contained in the vaccine. That evaluation demonstrated cross-protective efficacy of four cancer-causing HPV types not included in the bivalent vaccine – HPV types 33, 31, 45 and 51 – in different study groups that were representative of diverse groups of women.

A review and meta-analysis by Malagon et al (2012) analyzed data from comparable populations between the Future I/II studies and the PATRICIA trial with respect to cross-protection. Compared with the quadrivalent vaccine, the bivalent vaccine efficacy was higher against persistent infection and CIN2+ that was associated with HPV types 31, 33, and 45. Extended analysis suggested waning cross-protection against HPV 31 and 45 with the bivalent vaccine.

Although some level of cross-protection has been demonstrated for the existing HPV vaccines, the mechanism conferring this cross-protection remains unknown. The current evidence suggests that cross-protection
efficacy against non-vaccine HPV types is less robust and reliable than that observed for vaccine types, and that the level of cross-protection is highly influenced by the presence of co-infections. No indications for cross-protection for the existing HPV vaccines have been acknowledged by Health Canada. Taken together, these findings support the need for vaccines with broader coverage, but no data regarding the nonavalent vaccine is available yet on cross-protection. Long-term follow-up studies may provide important data in the future.

Detailed references for Q42 (180, 223–227) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

**Q43 Should HPV testing be done before vaccination?**

- No, HPV testing is not indicated and not useful before HPV vaccination.

HPV testing is not necessary prior to vaccination. Individuals who are sexually active or show evidence of prior infection should be counselled that the vaccine might be less effective when exposure to HPV has occurred before vaccination. The need for regular cervical cytology screening should be emphasized.

Type-specific HPV DNA assays to determine the presence of current or previous HPV infection have been approved for use with women in certain situations in conjunction with Pap tests, usually to assess the need for further tests and management after abnormal screening results. No HPV DNA tests have been approved for use with men.

The likelihood is very low that a woman will have been infected with all HPV types targeted by the bivalent or the quadrivalent vaccine, and so would not benefit from an HPV screening test. Therefore, HPV testing is not recommended before vaccination.

Detailed references for Q43 (2, 28, 86, 228) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.
SCREENING
Will prophylactic HPV vaccination reduce or eliminate the need for cervical cancer screening?

- Cervical screening remains a priority for the vaccinated population.
- Individuals remain at risk for abnormal Pap tests and pre-cursor cervical lesions caused by HPV types not covered by the vaccine.
- Screening practices will initially be the same. It is possible that screening may evolve over time towards delayed screening, longer screening intervals and using tests with greater sensitivity, i.e., HPV DNA testing.

Current vaccines do not protect against all HPV types. As more protection evolves over time, recommendations will align with new data.

The impact of HPV prophylactic vaccines on screening will depend on the prevalence in the population of HPV types covered by the vaccines, and on the proportion of the population who are vaccinated. Provided all women are optimally vaccinated, it can be expected—based on the known epidemiology and distribution of HPV types 16 and 18—that cervical cancer rates will be reduced by 65% to 77%, HSIL by 41% to 57%, LSIL by 15% to 32%, and ASCUS/ASC by 8% to 19%. For the quadrivalent vaccine, a further 10% reduction in cervical lesions and a reduction of over 90% in genital warts can be expected from the contributions of HPV 6 and 11 to these lesions.

The same screening process must be applied at this time to both vaccinated and unvaccinated individuals because HPV types that are not prevented by vaccines cause a proportion of cervical lesions. Practitioners will need to educate patients about this to prevent complacency and false reassurance.

Pap tests

Current screening practices rely on cervical cytology which has low sensitivity (48–50%). Pap tests (cytology) therefore need to be repeated on a regular basis to increase the chance of detecting a lesion. Successful screening is highly dependent on such issues as sampling, slide preparation, and cytological interpretation.
Opportunities for change in screening practice

With improved understanding of the natural history of cervical lesions and their progression to cancer, there is an opportunity to move to a new paradigm for screening. The major pre-cursors of cervical cancer are persistent oncogenic HPV infection and HSIL. Less frequent screening with a highly sensitive test, such as the HPV DNA test, could represent an evolving strategy for the growing vaccinated population. Such changes would ideally occur within the context of an integrated registry that includes data regarding screening, HPV tests, vaccination status, pathology results and cancer. All this is essential to address issues of vaccination and screening compliance and for evaluation of screening strategies.

Detailed references for Q44 (2, 28, 129, 130, 229, 230, 231) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

Will an HPV test replace current screening by Pap tests? If so, how will we screen?

- Screening is still required but paradigms will change and potentially be customized for vaccinated and unvaccinated women.
- Age to start screening will likely be later.
- Screening intervals will likely lengthen as HPV tests are integrated into population-based screening programs.
- Once HPV tests are used for primary screening, Pap tests will likely be used as a triage mechanism after a positive HPV test to assess whether atypical cervical cells are present.

Clinicians are referred to screening guidelines appropriate to their respective province or territory, and to other resources listed at the end of this book, including the National Advisory Council for Immunization and the Canadian Partnership Against Cancer. Also, the World Health Organization released new recommendations in December 2014 regarding primary and secondary prevention of HPV-related diseases.
Despite significant decreases in rates of squamous cell cervical cancer, the incidence of adenocarcinoma and adenosquamous carcinoma has either plateaued or increased in several jurisdictions. Cytology screening is generally less effective in detecting the latter two cancers of the cervix than squamous cell carcinoma.

A revised screening paradigm that includes HPV testing as the primary screening event, combined with cytology for secondary triage, could potentially reduce the incidence of, and mortality from, both adenocarcinoma and adenosquamous carcinoma.

Several studies have demonstrated the improved sensitivity of primary HPV testing over cytology screening. This finding, along with the high negative predictive power of an HPV test, allows for increased screening intervals. However, the specificity of HPV testing is less than that of cytology. In young women the high prevalence of hrHPV reduces the advantage of HPV-based screening as more women would be referred to colposcopy. A triage of HPV-positive patients using cytology, or another discriminating test, could help determine referral criteria to colposcopy and/or follow-up.

Detailed references for Q45 (2, 231–235) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

Q46 What is the best way to screen young women who have been vaccinated?

- All provinces recommend standard screening protocols for both immunized and non-immunized women.
- As new data emerge, recommendations will align with new evidence.

Currently there is no change in screening recommendations for immunized or non-immunized women. It is possible that guidelines for screening initiation and screening intervals will differ for immunized women. With the high volume of emerging evidence, change is inevitable, but policy decisions typically lag behind new discoveries. It is important that provinces create adequate data linkages with screening programs, including cytology and histology results, as well as immunization and cancer registries.
Worldwide, national and international agencies are working to implement vaccination and screening guidelines and initiatives that are relevant locally within available resources. Hopefully this will lead to a reduced burden of HPV-related diseases in both high- and low-income countries.

Please see the Resources section at the end of this book for current provincial and territorial screening guidelines.

See reference 236 for Q46 in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

Is HPV testing recommended in men?

- HPV tests have not been approved for routine population-based screening of men.
- HPV testing and anal cytology may be useful for assessing high-risk men, e.g., MSM and/or HIV+ males.

No HPV test has been approved for use in males. It is not recommended for men if their female partner is positive for HPV. Given that HPV is such a common virus in the general population, little benefit would be gained from testing males for HPV.

At the population level, HPV testing is primarily intended to screen for and/or treat cervical cancer in women. It is not recommended for men. For high-risk men, some clinicians and researchers conduct anal Pap and HPV tests to detect and treat high-grade AIN, and potentially prevent anal cancer.

Salit et al (2010) assessed the use of anal hrHPV tests and anal cytology among HIV+ MSM (N = 401). Cytology results were abnormal (HSIL: 12%; LSIL: 43%; ASCUS: 12%) in 67% of patients; histology was abnormal in 68% of patients (AIN2: 25%; AIN1: 43%). HPV was found in 93% of the study group, with multiple HPV types in 92% and hrHPV in 88%. HIV+ MSM have high rates of AIN2 and high-resolution anoscopy is necessary for optimal detection of abnormalities. Authors concluded that HPV tests and anal cytology have high sensitivity but low specificity for detecting AIN.

See reference 237 for Q47 in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.
Is there a role for anal screening and anoscopy?

- There is no role for routine screening at the population level.
- However, researchers are investigating the role of anal screening and anoscopy for high-risk groups, e.g., those with a history of VIN and/or AIN.
- Women with VIN are more likely to have AIN.
- Based on clinical consensus, HPV vaccine is a good option for high-risk groups.

A recent survey of clinicians (n = 82) providing services at anal cancer screening clinics (n = 80 clinics) around the world provided interesting data on their screening practices. The response rate was low (~27%) in this survey by Patel et al (2014). More than one-third of clinics offered unrestricted access to screening; the remainder offered screening based on abnormal anal cytology or HIV status. Given that anal cancer has been rare in the general population, a role is not likely for a population-based anal screening program. Nevertheless, exploring options for access in research settings and for high-risk populations seems appropriate for MSM, HIV+ individuals, anyone who has receptive anal intercourse, and women with CIN3+ or vulvar cancer.

See also Q4.

Detailed references for Q48 (46, 238, 239) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.
Contemporary Clinical Questions on HPV-Related Diseases and Vaccination

DIAGNOSIS & FOLLOW-UP
Q49 How do you get HPV-related oral disease? Is there any indication to screen for oral HPV or associated disease?

- Oral HPV-related disease is transmitted by oral sexual contact.
- There is no approved screening test.

HPV-oropharyngeal squamous cell cancer (HPV-OSCC) is related to oral sexual behaviour. A strong increase in incidence of HPV-OSCC in the USA is reportedly a function of changes in sexual behaviour in the last 50 years. Variations in prevalence by race, age cohort and gender may be associated with different sexual behaviours in these groups. Given that HPV infection is a pre-cursor to HPV-OSCC, it is important to define the risk factors, natural history of infection persistence, transformation, and progression to cancer. Knowledge is essential as to what differentiates those who clear the infection and those who do not. Further study is needed to define these parameters to inform approaches to effective screening, prevention and education for the general public.

The Canadian Dental Association recommends that people contact their dentist about lesions or changes in the lips, tongue or mouth. The US Preventive Services Task Force found that evidence was insufficient to support screening at the primary care level, but their recommendations did not apply to other health care providers. They suggested that the clinical experience of dentists and otolaryngologists would be the best basis for screening decisions related to patient history and other factors.

Detailed references for Q49 (53, 54, 240–242) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

Q50 What is the best test of cure after treatment for cervical dysplasia?

- HPV testing for hrHPV is one mechanism for follow-up after treatment for cervical dysplasia.
Whenever approach is used, women’s attendance at follow-up visits is of primary importance given that “loss to follow-up” is far too frequent among women with abnormal screening results by Pap tests.

Many colposcopy guidelines including Canada, USA, Australia and the UK recommend HPV testing as a test of cure after treatment for dysplasia. This is based on retrospective evidence and relying on the negative predictive power of an HPV test.

Several studies investigated the persistence of hrHPV after treatment. It is clear that persistence of the same HPV types is common. This has raised the possibility that HPV genotyping may be beneficial in identifying treatment failures; however, genotyping is not clinically available in Canada.

Receiving the quadrivalent HPV vaccine immediately after treatment by LEEP may prevent the recurrence of CIN2/3. (Question 19)

A current randomized controlled trial has been designed in Canada to compare colposcopy and HPV testing in the follow-up of high-grade dysplasia treated with LEEP (Mayrand et al, 2014).

Detailed references for Q50 (147, 243, 224, 246) can be found in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

Q51 How should the clinician treat those who are persistently positive for oncogenic HPV?

- Annual follow-up with cytology and repeat HPV testing is the ideal approach, with referral to colposcopy for persistent infections.
- Most jurisdictions do not yet test for oncogenic HPV, so most individuals are referred back to regular screening. If individuals adhere to recommended screening protocols, those with any subsequent abnormalities would be referred for colposcopic examination.

There are no guidelines for treating persistent HPV; however, those with persistence with the same hrHPV genotype are at increased risk of developing a high-grade lesion. Clinician consensus suggests annual follow-up at a colposcopy clinic.
A review of Kaiser-Permanente data by Katki et al (2013) showed that the five-year risk of CIN3+ risk after the second HPV-positive / Pap-negative test was 7.4%; hence, colposcopy was recommended in the 2012 ASCCP management guidelines. It is notable that this risk was greater than the risk of CIN3+ being detected on an LSIL Pap test result, which at present warrants referral to colposcopy. In the scenario of a negative Pap test with persistent HPV (if type testing is done and HPV 16 and 18 had/have persisted), careful colposcopy must be performed because of an increased risk of invasive disease.

See reference 247 for Q51 in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) available on the GOC corporate website at www.g-o-c.org.

If patients have had SIL/CIN and been treated by LEEP, will they still have the virus? Can they transmit it to their partners? Will their partners re-infect them each time they have sexual contact? Does vaccination help?

- Most women do not have detectible HPV after treatment for cervical SIL/CIN.
- Although most couples share HPV types, re-infection remains possible, but it is still unclear.
- Vaccination before or after treatment has been shown to reduce recurrence of CIN.

Many jurisdictions recommend HPV testing after a LEEP procedure as a “test of cure”, women who are HPV negative post treatment are at low risk of persistent/recurrent disease (Question 50). In Korea, 672 women were treated by LEEP for CIN2/3. At follow-up with cytology, HPV testing (HCII) and genotyping (HD-C–PCR-based DNA microarray system), 37 (5.5%) experienced a recurrence and tested positive for the same hrHPV before and after treatment. It should be noted that in this study, persistent infection with HPV 16 and 18 was highly linked (p < .05) to recurrence or residual disease, and should be viewed as a risk factor for recurrence of CIN2/3.

Transmission of HPV between sexual partners has been investigated in the HITCH study from Montreal (Burchell 2011). Sexually active partners usually have the same HPV types. Transmission from male to female, and female to male, included from 3.5 to 4.5 HPV types per 100 patient months. It is likely
that in a stable relationship, partners had similar HPV infections prior to treatment. It is possible that reinfection occurs from their partner.

Kang et al (2013) investigated the potential benefit of HPV vaccination post treatment. They reported that immunization with quadrivalent vaccine after LEEP may prevent a recurrence of CIN2/3. They followed 737 women between 20–45 years of age who were diagnosed with CIN2/3 and treated by LEEP. Women were offered the quadrivalent HPV vaccine after treatment. Of the total cohort, 360 accepted the vaccine (vaccine group) and 377 declined (non-vaccine group).

Risk of recurrence was higher for those women who:
1) were not vaccinated (HR = 2.840; 95% CI: 1.335–6.042; *p* < 0.01);
2) had cone margin involvement (HR = 4.869; 95% CI: 2.365–10.221; *p* < 0.01); or
3) had positive endocervical involvement (HR = 3.102; 95% CI: 1.363–7.062; *p* = 0.01).

No differences were noted between those who were cured and those who experienced recurrence with regard to age, previous cytological abnormalities and CIN grade at the time of the LEEP.

**Q53** Should a person whose partner has had genital warts have an examination of the oral cavity and throat by an ear, nose and throat (ENT) specialist?

- Current recommendations do not suggest ENT examination for potential and known contacts.
- There is no proven screening test for oral HPV and related diseases.

There are no current recommendations, but clinician consensus is that partners do not need to see an ENT specialist in this situation. Genital warts seldom progress to cancer; most are caused by HPV 6 and 11 — two HPV types that are included in the quadrivalent and nonavalent vaccines. Vaccination is probably the best preventive strategy.

See also **Qs 4, 5 & 27**
**RESOURCES**

**National**

*Canadian Immunization Committee*
Recommendations for Human Papillomavirus Immunization Programs.

*Canadian Partnership Against Cancer*
Prevention and Screening
http://www.partnershipagainstcancer.ca/what-we-do/prevention-and-screening

Cervical Cancer Control
http://www.partnershipagainstcancer.ca/resources-publications/

*The Society of Gynecologic Oncology of Canada*
www.g-o-c.org

GOC, SOGC, SCC and Family Physicians of Canada Joint Position Statement: Safety of Gardasil® HPV Vaccine
Summary of Canadian Immunization Committee (CIC) recommendations for HPV immunization programs:

National Advisory Committee on Immunization:
Update on Human Papillomavirus Vaccines

Society of Canadian Colposcopists
Colposcopic Management of Abnormal Cervical Cytology and Histology

Society of Obstetricians and Gynaecologists of Canada
Clinicians:
http://sogc.org

General Public:
http://sexualityandu.ca
http://hpvinfo.ca

Provincial & Territorial
Cervical Cancer Screening Programs
(and related screening guidelines)

Alberta
Program: http://www.albertahealthservices.ca/services.asp?pid=service&rid=1007675


British Columbia
British Columbia Centres for Disease Control:
Vaccine Resources for Health Care Professionals
http://www.bccdc.ca/imm-vac/VaccinesBC/HPV/default.htm

Health Care Professionals Q & A on HPV
http://www.immunizebc.ca/diseases-vaccinations/HPV/HPV-Vaccine-faq-0

Program: http://www.screeningbc.ca/Cervix/ForHealthProfessionals/Default.htm


Manitoba
Program: http://www.cancercare.mb.ca/home/prevention_and_screening/professional_screening/cervixcheck


New Brunswick
Program: http://www2.gnb.ca/content/gnb/en/departments/health/NewBrunswickCancerNetwork/content/NewBrunswickCervicalCancerPreventionScreeningProgram.html

Guidelines (2011): http://www2.gnb.ca/content/gnb/en/departments/health/NewBrunswickCancerNetwork/content/ClinicalPracticeGuidelinesForCervicalCancerPreventionAndScreeningInNewBrunswick.html

Newfoundland and Labrador

Northwest Territories


Nova Scotia


Nunavut
Program: Program information not available

Guidelines: Guideline information not available

Ontario
Program: https://www.cancercare.on.ca/pcs/screening/cervscreening/


Prince Edward Island
Program: http://www.healthpei.ca/papscreening


Quebec
Program: https://www.inspq.qc.ca/en/publications/1081


Saskatchewan

Yukon
Program: Program information not available
Guidelines: Guideline information not available

International

World Health Organization

Centres for Disease Control and Prevention (USA)
http://www.cdc.gov/cancer/gynecologic/

London School of Hygiene & Tropical Medicine and PATH
http://www.rho.org/HPVlessons-video
www.rho.org/HPVlessons
Abbreviations

AAHS  adjuvant, aluminum hydroxyphosphate sulfate
ACIP  Advisory Committee on Immunization Practices
AE  adverse event
AEFI  adverse events following immunization
AIN  anal intraepithelial neoplasia
APC  annual percentage change
ASCP  American Society for Colposcopy and Cervical Pathology
ASC-H  abnormal squamous cells
ASC  atypical squamous cells
ASCUS  atypical squamous cells of undetermined significance
CDC  Centers for Disease Control and Prevention
CI  confidence interval
CIN  cervical intraepithelial neoplasia
CPAC  Canadian Partnership Against Cancer
DPTP  diphtheria, pertussis, tetanus, polio
ENT  ears, nose, and throat
EUROGIN  European Research Organisation on Genital Infection and Neoplasia
FAQ  frequently asked questions
GMT  geometric mean antibody titer
GOC  The Society of Gynecologic Oncology of Canada
HAART  highly active antiretroviral therapy
HCII  Hybrid Capture Test II
HEPA  high-efficiency particulate air
HGAIN  high-grade anal intra-epithelial neoplasia
HIV  human immuno-deficiency virus
HIV+  HIV positive
HIV-  HIV negative
HPV  human papillomavirus
HPV+  HPV positive
HPV-  HPV negative
HPV+ OSCC  HPV-positive oropharyngeal squamous cell carcinoma
hrHPV  high-risk human papillomavirus
HSIL  high-grade squamous intra-epithelial lesion
IARC  International Agency for Research on Cancer
IPV  International Papillomavirus Society
JCVI  Joint Committee on Vaccination and Immunisation
LEEP  loop electrosurgical excision procedure
LSIL  low-grade squamous intra-epithelial lesion
MSM  men who have sex with men
NACI  National Advisory Committee on Immunization
OPC  oropharyngeal cancer
PCR  polymerase chain reaction
PHAC  Public Health Agency of Canada
RCT  randomized control trial
RRP  recurrent respiratory papillomatosis
SCC  squamous cell carcinoma
SIL  squamous intra-epithelial lesion
STI  sexually transmitted infection
VAERS  Vaccine Adverse Event Reporting System
VE  vaccine efficacy
VIN  vaginal intra-epithelial neoplasia
VLP  virus-like particles
WHO  World Health Organization
References

A complete reference list is available in Contemporary Clinical Questions on HPV-Related Diseases and Vaccination (Comprehensive Version) that can be accessed for free at www.g-o-c.org.