Answers by Dr. Catherine Popadiuk

to Questions asked during CIDC's Oct. 31, 2019 webinar:

HPV-based Cervical Screening: Why is NOW the time?

1. Would you recommend that we offer men over 25 Gardasil 9? or if men ask for it to prescribe it?

Men benefit from HPV vaccination directly to prevent HPV 16 related head and neck cancers, anal cancer and penile cancer. The 6 other cancer-causing HPV types covered in the nonavalent vaccine (for a total of 7 including HPV 16) that protect against 90% of cervical cancer, are not prominent in Head and Neck, anal and penile cancer and thus not necessarily as beneficial to men as HPV 9 is to women.

By vaccinating men with 9valent vaccine, they can help protect female partners directly and through herd immunity indirectly in the population. Where vaccination rates in female populations are not high (less than 90%) males have a greater impact towards herd immunity than if a greater proportion of females was vaccinated.

In the most recent NACI statements, there is no cutoff age to receive the HPV vaccines in men or women. Although the HPV vaccines are "recommended" to the age of 26 years old, the Gardasil or Cervarix vaccines "may be administered" to females and males over 26 years of age. There is no formal cut off if a health care provider and individual feel that he/she may derive benefit from HPV vaccination has approved HPV vaccination given their particular circumstances and risk. A 3-dose schedule is required in men and women over 15 years of age as well as in those who are immunocompromised.

2. I didn't know of self-sampling for HPV; have any had positive results from patients performing this and would you repeat the test in the office if so?

Presently HPV Self Sampling is offered in Canada for research purposes or as part of pilot study programmes. It has been available to the public online but at a significant cost of $100. If a patient is HPV positive, she will require follow-up which means a pap test. Most likely the HPV self sample was done on a liquid based specimen, and thus a reflex Pap test may be able to be interpreted from the specimen. Nonetheless, the patient requires follow-up and a visit with a health care provider. For women who do self sampling and have an HPV negative result, because HPV testing is not the standard screening test in Canada, they are encouraged to still see a health care provider and have a pap test so they are not lost to follow-up from a screening program registry, and for quality assurance purposes.

Eve Medical offered HPV testing to women who could purchase it online but the tests are presently on back order.

3. What's the role of HPV Vaccine in patient having colposcopy?

Patients who have had colposcopy and have not received the HPV vaccine, should be offered HPV vaccine as clinical trials have shown that vaccination does help decrease the chance of further abnormal pap tests and need for colposcopy and treatment. The Nonavalent vaccine is now available whereas previously, the quadrivalent and bivalent vaccines were used for vaccination. These vaccines covered HPV 16 and 18 high risk types. The nonavalent covers an additional 5 high risk HPV types increasing protection to almost 90% of cervical cancer-causing HPV as opposed to the 70% caused by HPV 16 and 18.

Women who were vaccinated by the original vaccines covering HPV 16 and 18 types are not protected against the other 5 HPV types in the nonavalent vaccine and thus should consider being vaccinated with the nonavalent vaccine. Unfortunately, a full 3 injections are required for full protection in older girls and women even if they have previously had the first-generation vaccines.

4. With the rise of Oral Cancer numbers, would oropharyngeal testing for HPV be beneficial as well?

There is no simple screening test for oropharyngeal cancer. The problem with swabbing for Oral HPV, similar to cervical HPV testing, is that the presence of HPV does not necessarily signify disease. The HPV may be transient and not persistent or associated with disease.

5. In current political climate, what is likelihood that governments will fund HPV primary? It is clear that most patients don't want to pay the additional cost

Agree that patients should not bear the costs of HPV testing. When politically useful, it will be funded. Personally, I feel the federal government should show more leadership in this area as the previous government that funded $300 million towards HPV vaccination as a strategic health directed initiative.

6. How will the public be educated to continue to go for check-ups for other reproductive issues i.e. STD's if Canada moves to a 5yr recall cycle (or even 10 yr.)

With the Choosing Wisely campaign there is an opportunity to educate on the need for less frequent testing for screening while drawing attention to important and timely STI and reproductive health care. It will be decades before the vaccinated generation of girls moves through their lifespan where screening every 10 years would make sense and be safe. There is thus time to prepare for that generation. Changing to five-year intervals with HPV testing will be difficult to persuade health care providers and women that this is safe.

7. What do you say about internal CELLULAR control to assure that the sampling was well done? Specifically, for auto-sampling patient. To avoid false positive results?

The DNA type of HPV tests appear to be safe and sensitive for self sampling specimens. The tests themselves have an internal control for cellularity. This was further studied with the beta globin detection in the HPV Focal Study in British Columbia. Adding further internal control did not detect more positive results.

8. What will be the role of cytology in HPV primary screening model?

Cytology is meant to be a secondary triage test after an HPV positive result. Depending on the HPV test type, the Pap test may be done for all HPV positive results and where abnormal the patient may go on to colposcopy. Where HPV testing can distinguish HPV 16 and or HPV 18 and or HPV other, the HPV 16/18 patients may go directly to colposcopy and the HPV other patients would have pap cytology.

9. Does woman open to pay to get the PCR test or they will wait until it's paid by government?

Women in Quebec can purchase HPV testing as can some women in Ontario and possibly other provinces. One is encouraged to explore services and prices available in their respective regions. Some HPV testing is paid for by hospitals and governmental funding agencies usually for follow-up post colposcopy LEEP treatment and as triage of mildly abnormal pap tests (ASCUS, LSIL in Alberta?)

10. Is a national screening plan with HPV testing an option for the recent government?

Certainly the Federal government has encouraged organized cervical cancer screening since 1976; funding it has been another story. The present federal government is seen as being gender conscious and supporting women. They respond to persuasive arguments and lobbying for important initiatives.

11. Can HPV-screening detect late stages of cancer, e.g. with women who did not attend screening for a long time. Or would cytology or co-testing be more sensitive in these cases?

HPV testing can detect HPV wherever it is present. If someone has a large cancer, it should be obvious to detection and be seen by visual inspection on speculum exam or clinical exam and imaging. But as cancer develops from pre-cancer, it is not unusual for HPV to no longer be expressed and thus to have a negative HPV result. Pap tests are also said to be negative 50% of the time with an obvious cancer. Good clinical intuition and judgment is the most sensitive test for large cervical cancer over any screening test: HPV and Pap cytology.

12. Is it not true that most new cases of cervical cancers are from patients that have not been screened regularly or screened at all? Why not put the emphasis on creating programs that get more women tested firstly before we change from Pap smears?

Absolutely. Up to 50% of cervical cancer is diagnosed in women who have not been screened in over five years or more, or never. Provincial screening programs do their best to reach these women but funding is limited. Private companies promoting HPV vaccination and HPV testing, both important and admirable goals, have more resources at their disposal to share information about new tests and preventive strategies than fiscally limited public health organizations that often see their funding cut before direct clinical service budgets.

13. I thought HPV is not recommended for patients under 30.

Women under 30 years old have been more likely to have transient HPV infections with the onset of sexual activity and new partners. But the generation of vaccinated school girls are now 25 years old and no longer manifesting this higher rate of HPV positivity thus HPV testing in this group of young women would show much less HPV positivity. The women 26 to 29 years old would have benefited from HPV catch up vaccination and some benefits of herd immunity, but the true decrease of HPV positivity in this population has not achieved the same maximal benefit in those up to 25. Women over 30 who are HPV positive, most likely have persistent HPV infection and are a small proportion of that population, thus making HPV testing cost effective and sensitive for true precancer.

14. Has anyone looked into the potential impact of HPV primary on detection of glandular malignancies? There are several endometrial cancers detected on Paps as incidental findings.

HPV testing has been shown to be superior over cytology testing to detect cervical adenocarcinoma but endometrial cancers are not HPV related cancers. Cytology has the potential to identify endometrial problems if there are atypical endometrial cells on Paps (or atypical glandular cells that are not HPV positive) in any woman, or endometrial cells present when they should not be there such as in postmenopausal women or during the wrong time of the menstrual cycle, especially in women over 45.

If primary HPV testing is done for cervical screening, then cytology identification of coincidental other problems, such as endometrial cancer or hyperplasia/atypia will not be detected unless the woman is complaining of symptoms (abnormal bleeding etc.) or is HPV positive. The endometrial cancers detected through cytology are an extra benefit from cervical pap testing. Endometrial cancer screening through endometrial biopsies or cytology has not been shown to be cost effective. Perhaps in the future an argument can be made to screen high risk patients such as those with PCOS, or obese women. Women with the Lynch mutation are considered

high risk and should have endometrial sampling until they can have definitive hysterectomy and BSO for endometrial and ovarian cancer prevention.

15. Just wondering why HPV testing would be such a challenge when the use of the broom will be the same tool for specimen collection.

The cost of the lab HPV interpretation is still more expensive than what is charged for pap cytology testing. With higher volumes of women being tested, the costs of testing should decrease making it more cost effective.

16. How much resistance is there to the HPV vaccine?

This depends on where one looks. In some provinces and communities, HPV vaccination is embraced. Where there is vaccine hesitancy among a group of people due to perceived dangers of vaccines to cause other medical problems (mis information), there is great resistance. Religious belief, culture and general attitudes towards sexual activity in youth, also impact on acceptance of the HPV vaccine in particular.

17. Germany has decided to evaluate co-testing in the next 6 years - What is your personal opinion on co-testing?

In the United States co-testing has been the standard for several years and they have large studies describing the benefit of co-testing every 5 years over pap screening every 3 years or primary HPV testing every 5 years. Kaiser Permenante in California published their experience and quantified the absolute benefit of co-testing over HPV testing. 1 more cancer would be detected among 1 million women. This was not found to be cost effective.

That being said, transitioning directly from cytology to HPV testing is very difficult as seen by the reluctance by labs and their personnel to move in this direction, and in countries where the change was made, Australia for example. Other countries are transitioning with pilot studies and smaller roll outs.

In my local lab in Newfoundland and Labrador, the cytologists are more comfortable adding HPV testing to various pap results, for example AGC (as well as ASCUS). The cytology physicians have tried various HPV type assays and they perform slightly differently. The differences cause discomfort about missing a patient with pre-cancer especially if a pap test may have picked up something that an HPV test may have not. Locally, the cytologists are more comfortable with co-testing as a step towards primary HPV testing. Whether the funder will support this strategy is yet to be seen. A business plan will have to be put forward. The benefit arguably would be potential decrease of women requiring colposcopy resources versus primary HPV testing in the short term.

18. Is there any correlation between HPV and Breast Ca and if so what is it?

There is no correlation at this time between HPV and certain types of breast cancer as is seen with anal and head and neck cancers. There is some early research that HPV may be present in some lung cancers but this work is premature. Similarly, HPV could be spread with oral contact on the breast, but whether HPV spreads to ducts and lobules in any clinically relevant manner, is yet to be determined.

19. What are your thoughts about the Netherlands model? Do you think screening every 5 to 10 years is adequate?

The Netherlands is more comfortable with detecting small cancers that may occur with a longer interval between screens. Canada has had a more aggressive approach to screening and treatment of precancer to prevent the development of any invasive cancer, even small ones. A 10-year interval in the present state would not be well received in Canada.

20. Australia started its vaccination program offering to both boys and girls. We did not in BC. How do we ensure that boys who were started a few years later know they are not covered and also how do we ensure that girls as women know if they got the quadrivalent vaccine?

These are excellent questions and concerns and speak to the need for accurate and widespread education and policy at provincial and federal levels. As our youth and younger generation are better versed and educated through school and several media in the deleterious and imminent effects of climate change, so too should they be informed of the importance of vaccination for the spectrum of communicable diseases from measles to HPV. The widespread vaccine hesitancy movement can only be addressed with persistent accurate evidence based messaging.

And the provinces and territories should have the adequate resources to link cervical screening data with HPV vaccination history. Girls and women should also have easily available individual information about their vaccination records which presently is not done available in most provinces. Manitoba is an example of a province with linked HPV vaccine and screening records. There must be a political will to fund this work.

21. Would you recommend self-sampling as an option even for those who currently are being screened regularly?

HPV self sampling is not yet available in provinces or territories beyond pilot studies and personal choice for women wishing to purchase a self sampling kit from Eve Medical (presently on back order). Self sampling may be seen as an attractive option for women who are too busy to attend a health care provider appointment or where HCP is not available but it is not a

substitute for the value of the counseling and human interaction and education with a HCP who can respond to questions and concerns, and assess for other health risks at the same time. For those who are currently screened regularly with pap tests, self sampling with HPV will not necessarily add more information to a treatment pathway other than the knowledge of one's HPV result that could complement a pap result. It cannot replace the pap test in the present environment. Women who choose to do an HPV self sample out of the provincial territorial screening programme, may miss the benefit of being included in a registry system for surveillance, recall and invitation to screening. It can also be complicated to reintegrate into the system with an HPV positive result. If one is positive for high risk HPV 16 or 18, or other, she will require further testing with colposcopy or pap test. If the public system does not yet have established algorithms for follow up, a woman with a self sampled HPV result may have difficulty integrating into the system seamlessly. She may encounter some confusion from providers who are not acquainted with HPV testing algorithms.

22. Why screen? Why cost of screen? why not just vaccinate?

Screening for cervical cancer with pap tests has been found cost effective and a public good since the 1950s. The pap test could prevent women from developing cervical cancer if precancer could be identified and treated. Enough women were at risk that pap tests were cost effective to offer to all sexually active women at a regular interval. With the advent of HPV vaccination, the risk of developing cervical cancer will decrease from 70 to 90% depending upon which vaccine girls received before the onset of sexual activity. As decades pass and more vaccinated cohorts of women make up the entire female population, the risk of developing cervical cancer will likely be so small that it will not be cost effective or of significant risk to offer screening to a population of women with the frequency that is happening today. It may be that vaccinated women will require from 2 to 4 screens (likely HPV testing) over a lifetime, or hopefully cervical cancer will be eliminated such that it will be such a rare cancer, screening will not be required.

23. Is it beneficial for all labs to use the same HPV method when primary HPV testing is implemented?

One cannot dictate local circumstances and decision making in the context of varying human, technical and capital resources, but generally, standardization and seamlessness is easier for systems than fragmented different systems. For example, having one EMR for a large region or provinces, makes for better communication and enhanced safety than several separate silos.

24. The pap test, isn't sufficient to detect and prevent HPV. We should include the DNA testing also? Is that right?

The sensitivity of the pap test is less than the HPV test. But specificity of the HPV test is poorer than a pap test. Several large RCTs have shown that HPV testing is better able to detect more CIN2+ and cancers than pap testing sooner in a screening cycle, thus the change to using primary HPV testing for cervical cancer screening in countries such as Australia, the UK, Netherlands and various other European countries. As the proportion of HPV vaccinated women increases with time, the sensitivity of the pap test will not be adequate for screening and HPV testing will be better. The poorer specificity of HPV testing as a primary screen will improve as women who are vaccinated are less likely to have HPV and its deleterious precancers and cancer. Transient HPV positivity in women under 30 makes HPV testing difficult as a primary screen. But as these women are vaccinated, they are less likely to manifest high risk HPV types with an HPV test. And it may be that screening will not be offered to vaccinated women until later than 21 or 25 years.

25. When should we vaccinate an adult woman (25 and over)? The women not cover by the national immunization protocol.

    Case number 1: If the pap test were always negative, a regular partner (long term relationship), 35 years old?

    Case number 2: pap test positive, but treated, when she was 20 years old. Regular partner, 48 years old?

According to NACI, there is no cutoff age to receive the HPV vaccines in men or women. Although the HPV vaccines are “recommended” to the age of 26 years old, the Gardasil or Cervarix vaccines “may be administered” to females and males over 26 years of age. There is no formal cut off if a health care provider and individual feel that the woman may derive benefit from HPV vaccination given their particular circumstances and risk. Outside the public school based vaccination programme, individuals must pay for the vaccine or have insurance that will pay for this benefit.

For Case number 1, this patient appears to be at very low risk of having problems with cervical cancer based on the information today. But one doesn’t know risk in the future. Will she still be in a monogamous relationship the rest of her life with a partner singularly devoted to her forever? And with age one’s immune system diminishes so people who have never had problems before 50 years or older, can manifest abnormal pap results or screening tests despite normal screening history for decades. Ultimately the woman chooses her risk tolerance and ability to fund vaccination. Most important is continuing to attend screening for identification of problems, whether vaccinated or not.

For Case number 2, having had an abnormal pap result requiring treatment (LEEP?) at 20 years old, this woman is at higher risk than someone who has never had confirmed CIN2+. Women treated for CIN2+ are followed closely by screening programmes for up to 20 years as they are at risk of recurrent lower genital tract dysplasia, particularly if they smoke. HPV vaccination after CIN2+ treatment has been shown to be effective in decreasing the likelihood of further abnormal pap results, colposcopy and treatment. Vaccination with a nonavalent vaccine can prevent HPV infection of 7 high risk types of HPV. Although someone may have been exposed to one or more types, it is not likely that someone has been exposed to all 7. Furthermore, we do not know the details of the actual immune process in preventing recurrent HPV infection and downstream effects after lesion treatment, but benefit has been shown in this setting in vaccinated women, quoted as 65% in some studies. Again, if someone is unable to afford the HPV vaccine, ongoing screening and surveillance is available to all in the public system.