CERVICAL CANCER - Question and Answers for Practitioners

Q1
What usually happens once someone gets infected with HPV?

About 75-90 percent of HPV infections will clear within a year of initial infection.

If someone has persistent infection with a high-risk HPV type for more than 2 years, they have a higher cancer of progressing to cervical cancer. For someone persistently infected with HPV-16 after 3-5 years, they have a 40% chance of developing a precancer lesion.

Precancer is more likely in women infected with more than one type of HPV.

Early precancer changes can often be detected within 5 years from infection.

If someone has an untreated precancer, they have a 20-30% chance of developing cervical cancer within 5-10 years.

Q2
What is cancer screening?

Screening is a public health intervention used on a population at risk, or target population. Screening is not undertaken to diagnose a disease, but to identify individuals with a high probability of having or of developing a disease.

Women targeted for screening for cervical cancer may actually feel perfectly healthy and may see no reason to visit a health facility. For screening to be effective, accurate, easy to apply, simple, inexpensive, culturally acceptable, and safe, the disease screened must be common and should have a detectable preclinical stage, for which effective treatment should be available; a large proportion of people at risk should participate in screening, investigations and treatment; the local health services infrastructure should be sufficiently developed to provide the diagnostic, treatment and follow-up services.

Screening programs will only be successful if the following elements are present:

- High coverage (80%) of the population at risk of the disease;
- Appropriate follow-up and management for those who are positive on screening;
- Efforts to increase coverage will be wasted if those who test positive are not followed up correctly;
- Effective links between program components (e.g. from screening to diagnosis and treatment);
- High quality of coverage, screening tests, diagnosis, treatment, and follow-up;
• Adequate resources.

Q3
What are the U.S. recommendations for cervical cancer screening?

The following is a summary of various US organizations, because different organizations recommend different intervals. In general, cervical cancer screening should be done in any woman who has been sexually active for three or more years or is 21 years of age. The cervical cancer screening should be performed annually until around age 30, and then can be spaced out to every 2-3 years if the female is in a monogamous/low risk relationship. Cervical cancer screening can stop at age 65-70 if the patient has had a normal pap smear within the past 5-10 years. Additionally, cervical cancer does not need to be done in a woman who has had a hysterectomy for a problem other than cancer (fibroids, bleeding after child birth, endometriosis, etc.)

Q4
How do I get checked (screened) for cervical cancer?

Screening requires collection of cervical cells. This generally means lying on an examination table with the legs spread apart so that a trained health provider can insert a speculum into the vagina. This is important so that they can see the cervix and collect the sample properly. There are other self-sampling kits, which are being researched. These can be done in the privacy of your home.

Pap smears are used most commonly in the U.S. and are required for CDC-funded Breast and Cervical cancer screening programs. There are several ways to do pap smears (conventional slide or liquid-based). Each has its advantages. Liquid-based pap smears are more costly to process, but can give more consistent results regardless of the health provider’s skill. Liquid-based pap smears might reduce the need to repeat a pap because of an inadequate sample. Additionally, HPV-typing can be done on liquid-based samples.

Q5
What is Direct Visual Inspection (DVI) and how good is it in comparison to pap smears?

Cells that are heavily infected with HPV and precancer lesions can often be seen without a special microscope. A vinegar (acetic acid) or iodine solution is applied, which makes these abnormalities more easily visible.

In resource limited-settings, Direct Visual Inspection (DVI) after application of 3%-5% acetic acid has been demonstrated to be effective in reducing the incidence (new cases) of cancer by 26% (1-visit DVI in a 35 year-old woman) and was associated with lower total lifetime costs. Prevalence of precancer lesions was significantly lower at 6 and 12 months after a “screen and treat”, compared with delayed evaluation.
The sensitivity of DVI (the ability to detect high-grade cervical disease) is 0.80 and the specificity is 0.80 (the probability that the test will be negative in normal patients). Average positive predictive value is 0.14 and negative predictive value is 0.99.

In parts of Africa, China, Thailand, Italy, India and Guatemala, health providers treat any abnormal lesions that they see (usually with cryotherapy [liquid nitrogen]).

“Screen-and-treat” regimens using visual inspection have a tendency to “over treat” (by treating the low-grade lesions). However, in a setting where there is little or no follow-up possible, one could argue that it is better to treat all abnormalities seen.

Age 35 has been shown to be the ideal age for cervical cancer screening in resource limited settings.

Many research studies are ongoing worldwide to validate VIA/VILI as an appropriate screening methodology for resource limited settings. Many countries already use this as their primary method of screening for cervical cancer, using a combination of community-health workers and physicians.

ABNORMAL PAP SMEARS / PRE-CANCEROUS LESIONS

Q6
What are “worrisome” results on pap smears?

Pap smears scrape a small sample of cells from the cervix. A definite diagnosis of a precancer or cancer lesion requires a biopsy – a larger sample of cells that include more layers of the cervix.

A biopsy is the only way to tell for certain whether an abnormal area is precancer, true cancer or neither.

Squamous cell cancers are the most common type of cervical cancer. The LSIL and HSIL classification are for those. There are other types and their precancer lesions are also classified as LGIL or HGIL on pap smears.

“SIL” lesions (squamous intraepithelial lesions) can be categorized into low-risk (LSIL) and high-risk (HSIL) for progression to invasive cervical cancer.

“CIN” or cervical intraepithelial neoplasia are terms that should be reserved for biopsies.

Depending on the amount and quality of the biopsy sample, some pathologists may only be able to report the result using the SIL terminology.
HSIL implies CIN 2 or CIN 3. There is much more agreement among pathologists on what CIN 3 looks like (it is more reproducible) and CIN 3 lesions are much more likely to progress to cervical cancer. Therefore, all CIN3 lesions should be treated.

Q7
What type of monitoring should be done to prevent progression to cervical cancer?

In the U.S., some low-grade abnormal pap smears require a repeat pap in 4-6 months. High-grade abnormal pap smears require colposcopy and aggressive management

- Colposcopy is like a pap smear except that the health provider looks at the cervix through a special scope and applies vinegar or iodine to see abnormal lesions.
- It is still possible to miss a small area of abnormality with a colposcopy
- If an abnormality is seen, a biopsy or sample is taken from the area and sent to the lab.
- Once the results are available and depending on the result, the health provider may recommend immediate treatment (if a high-grade or precancer lesion) or may recommend no treatment and repeating a pap smear in 4-6 months.

In the U.S., a woman with a precancer lesion will typically have 6 office visits in one year:

- pap smear
- colposcopy and biopsy (2 weeks after the pap)
- treatment (1 week after the biopsy)
- repeat pap (4 months after the treatment)
- 5: repeat pap in 4 months or repeat colposcopy/biopsy/treatment if the repeat pap is still abnormal
- repeat pap in 4 months or repeat colposcopy/biopsy/treatment if the repeat pap is still abnormal
- repeat pap in 4 months or repeat colposcopy/biopsy/ treatment if the repeat pap is still abnormal
- After one year of normal pap smears is obtained, then a woman can return to annual pap smear testing

Q8
What types of treatments are recommended for precancer lesions?

If the biopsy shows equivocal (CIN2) or more definite (CIN3) precancer lesions, treatment is applied to the entire transformation zone of the cervix.

Cryotherapy (freezing the abnormal cells) with liquid nitrogen is almost as effective as LEEP or LLETZ to treat small precancerous lesions (90-95% effective). It can be provided without anesthesia or electricity. However, cryotherapy may miss deeper lesions. Cryotherapy destroys tissue, so there is nothing left to send to the lab for further analysis.

LEEP (loop excision electrocautery) and LLETZ (large loop excision of the transformation zone) require electricity to heat a thin wire, which cuts a cone of tissue out of the cervix. Local
anesthesia is required to the cervix. These can be done in outpatient settings and gives a large sample of tissue for further analysis. Sending a tissue is important if the LEEP/LLETZ is being used to treat early stage cervical cancer. In some studies, women who tested HPV negative after a LEEP did not have recurrence in 2 years.

**Q9**

What are the different treatment options (and possible side effects) for cervical cancer?

Depending on the stage of cancer and your other health conditions (such as severe heart or kidney disease), the doctor may recommend one or more of the following:

- Surgery (hysterectomy for stage IA1; radical hysterectomy and pelvic lymph node dissection for stage IA2-IIA; complete removal of most of the pelvic organs, including the bladder and parts of the rectum and colon for recurrent cervical cancer)
- Radiation therapy: beam or internal radiation to stop the cancer cells from growing
- Chemotherapy: medications that stop the cancer cells from growing
- Palliative treatment: aimed at relieving symptoms, not aimed at curing the cancer

For precancer and early cancers (Stage 0 or IA), surgery can be done by freezing (precancer or preinvasive cancer only), laser (preinvasive cancer), conization (precancer or early cancer).

Please refer to the American Cancer Society information for more detailed information on treatment options and side effects.

**Q10**

Once I am diagnosed with cervical cancer, what additional tests will be required?

Staging refers to the process of finding out how far a cancer has spread. This is important to direct appropriate treatment.

Cervical cancer staging is based on how big and deep the cancer extends into the cervix and surrounding tissues.

Depending on the clinical examination, additional tests to look into the bladder and rectum may be required. Sometimes a CT scan is required to look for distant metastases.

**Q11**

What is the chance of being alive 5 years after treatment for cervical cancer (also known as a 5-year survival rate)?

Stage IA (less than 5mm, can only be seen with a microscope): More than 95%

Stage IB1 (less than 4cm, can be seen without a microscope but hasn’t extended into other tissues): About 90%
Stage IB2 (more than 4cm, but hasn’t extended into other tissues): About 80%-85%
Stage II A/B (spread to tissues next to the cervix): About 75%-78%
Stage III A/B (spread to lower vagina or pelvic wall): About 47%-50%
Stage IV (metastatic): About 20-30%

HPV VACCINE

Q12
Routine HPV testing?

The common practice in the U.S. is to do HPV testing on some abnormal pap smears (ASCUS). This helps to determine appropriate management and treatment.

There is growing evidence to support doing HPV testing in conjunction with pap smears, especially in women over 30. This will help to identify the women at most risk for developing cervical cancer and who need more aggressive follow-up.

Research is being done to determine the usefulness of HPV testing alone.

The problem with HPV testing alone (without pap smears) is that the presence of a high-risk type (by blood tests) does not correlate well with cervical lesions.

Q13
Do I still need to get screened for cervical cancer if I received the vaccine?

Absolutely.

The vaccine is not 100% effective in preventing cervical cancer caused by the types in the vaccine. Additionally, the protection may not last forever and it does not protect against 30-50% of the other HPV types that cause cervical cancer.

It is possible for a vaccinated person to develop cervical cancer from another type of HPV.

- Because of this and because the vaccine is not perfect, educational programs, messages and public expectations need to be managed accordingly.

Cervical cancer screening and treatment precancer lesions is the only protection against the types of virus not in the vaccine and against existing infection with high-risk HPV types.

Q14
Is there more than one type of vaccine?
As of now, Gardasil is the one available in the U.S. It targets HPV 6, 11, 16, and 18

There are several more in development. One that targets 16 and 18 is currently approved for use in Australia.

Researchers are developing vaccines with more types, longer duration or lower cost, but they will not be available for many years (over 7 years)

Q15
What is the cervical cancer vaccine (Gardasil)?

Gardasil targets HPV 6, 11, 16 and 18

At best, it can protect against 90% of genital warts and 70% of cervical cancers

The best efficacy is in girls before they start having sex

It must be given in 3 doses, ideally over a 6 month period

It was primarily tested in girls age 9 – 26, but has also shown to be effective in preventing new infections in women up to age 45.

A recent study published in the New England Journal of Medicine, August 21, 2008, questions the cost-effectiveness of giving the vaccine to women over 18 years of age.

If someone is already infected with one of the virus types in the vaccine, the vaccine will still help to protect against the other types.

The vaccine does not treat existing HPV disease nor does it promote regression or healing of existing HPV disease.

Q16
How long does the vaccine protect women against the HPV?

Available research shows a good protection up to 5 years. Studies are being done now to determine how effective the vaccine is at 10 years after vaccination. Mathematical modeling suggests long-term efficacy.

Q17
How much does the vaccine cost?

In the US, the vaccine costs about $360 for all 3 shots if not covered by insurance or public vaccination programs
Additional costs include maintaining the cold chain (refrigeration), appropriate storage systems, delivering the vaccine to rural populations, developing programs that target preadolescent or adolescent girls.

Additional, related costs, include the costs of screening for cervical cancer (personnel, supplies, need to screen every 3 years (if following US recommendations, etc.).

Q18
Will the vaccine always be available for free - or reduced cost?

Unknown

Q19
Is the vaccine safe?

So far, over 12 million doses of Gardasil have been given and no rare, serious events have been seen with more frequency than what might be expected in a similar age group and community.

The HPV vaccine also appears to be safe in pregnancy, but pregnant women should not get the vaccine until after delivery. If she started the vaccination series and became pregnant, she should wait to complete the three-dose series.

To date, the vaccine does not cause any problems to the rest of the immune system and does not affect the efficacy of other vaccines administered at the same time (Hepatitis B vaccine has been the main one studied)

Q20
Are boosters safe and effective if needed?

Based on one small study, a booster dose given after 5 years appears to be safe and produces high levels of antibodies. Mathematical modeling suggests that protection is likely to be long lasting.

Q21
Do the vaccines provide cross-protection against a few related types, as previously suggested?

In some studies, there was cross protection in 30-40% for some other HPV types

Q22
What is the efficacy of fewer than three doses of vaccine?

Research is being done now to determine efficacy of 2 doses
Q23
Does the vaccine prevent infection in men, and reduce the transmissibility of HPV from men to their partners?

The vaccine is currently being tested in boys. There is insufficient information about the effect of the vaccine on transmission.

Q24
When immunity wanes and new infections occur, are the natural history of HPV16 and HPV18 infections and the related risks for precancer and cancer the same as in unvaccinated women?

In one trial immunization appeared not to affect the natural history of HPV infection. However, more research is needed to answer this.

Q25
What will be the effect of HPV vaccination on compliance with screening programs, which are needed for prevention of the 30% of cancers against which the vaccines do not provide protection?

Rates of screening may decrease if the public message of continued screening is not strong.

Q26
How great will the negative effect be of the reduced prevalence of HPV16 and HPV18 in post-vaccinated populations on the clinical performance and cost-effectiveness of screening assays and diagnostic procedures?

The effect is unknown, but as the prevalence of HPV16 and HPV18 decreases, the ability of a test to detect disease could be less. Screening protocols and recommendations will change over time.

Q27
Will prevention of infection with HPV16 or HPV18 alter the natural history of other carcinogenic types and the number of cervical cancers they cause?

Unknown at this time

Q28
Do these vaccines protect against other HPV-related cancers such as oropharyngeal and anal cancers?

Probably. However, because it generally takes longer for these cancers to develop, there is not yet enough data in this area.
In developing countries, where 80% or more of cervical cancer occurs, who can afford to get vaccinated, even with tiered pricing, in view of competing health priorities?

This can only be answered by each country.

A similar question can be asked for screening programs. What makes most sense given available resources?

DECISION-MAKING ABOUT A NEW VACCINE

Questions to Consider

The following questions could be considered when making a decision to start a new vaccination program:

What is the local burden of disease?

Have there been successful demonstration projects in similar settings?

What are global and regional WHO recommendations?

Are GAVI, UNICEF and bilateral donors supportive and willing to help fund the vaccination program?

Is there an appropriate economic model of cost-effectiveness and impact?

What is the level of knowledge about the disease and the vaccine in the medical community, the public and the media?

How much does the vaccine (and the program to implement it) cost?

Is it “affordable” to the country?

How much will it cost to sustain the program?

What other competing health priorities exists? Is there a greater need to expand or improve upon existing vaccine programs?

What are other countries in the region doing?

Do you have strong internal advocates to introduce and champion the vaccine to the public?

How successful has the vaccine been in the private sector?
For HPV, how do we improve cervical cancer screening in older women while protecting the younger generation with the vaccine?

For references for the Question and Answer Section, please click here.