Frequently Asked Questions on HPV

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HUMAN PAPILLOMAVIRUS (HPV)

1. What is HPV?

Human papillomavirus (HPV) is one the most common infections of the reproductive tract, responsible for a range of cancers and other conditions in both men and women. HPV is the cause of cervical cancer, the fourth most common cancer among women. It is therefore an important cause of morbidity and mortality in women, and an essential global public health priority. HPV is an extremely common virus that infects the skin and mucosa, and almost everybody in the world becomes infected with HPV at least once during his or her lifetime. There are many types of HPV, and while most of these infections do not cause any symptoms and will go away on their own, infection with certain high-risk types of HPV can worsen and develop into cancer. In addition to cervical cancer, HPV can also cause a variety of other health problems in both men and women such as multiple other types of cancer and genital warts., The virus can also spread through non-sexual means as well. There are safe and effective vaccines that prevent HPV infection.

2. How many types of HPV are there?

More than 100 types of HPV have been identified and more than 40 types that infect the genital tract. Some of them have been classified by the International Agency for Research on Cancer as “high risk” (carcinogenic) in humans. HPV-16 and HPV-18 are the two primary carcinogenic types, responsible for almost 70% of cervical cancers. HPV types 31, 33, 45, 52, and 58 together account for 15% of cervical cancers. HPV-6 and HPV-11 are the two primary “low-risk” (non-carcinogenic) types, which cause anogenital warts.

3. What are the biological characteristics of the HPV pathogen?

Part of the papillomaviridae family, human papillomavirus is small, non-enveloped, and contains a double-stranded DNA genome that infects skin or mucosal cells. This genome is composed of both early and late proteins which make up the characteristic icosahedral outer shell that holds the virus’s genetic material inside. The six early proteins (E1, E2, E4, E5, E6, and E7) manage regulatory functioning and virus replication; and the two late proteins (L1 and L2) are the major and minor viral structural proteins, respectively.

Over 200 HPV types have been identified and characterized based on the detection of the HPV DNA or mRNA of L1 (the major late structural protein). Papillomavirus types are usually classified by their probability of causing cancer. Low-risk HPV types are non-oncogenic, while high-risk HPV types are oncogenic. HPV types that have a higher potential to induce cancer or high-grade lesions are genetically related to each other, and cluster together on the phylogenetic tree.

4. How can HPV be contracted?

HPV is one of the most common sexually transmitted infection in the world and is usually-- though not always-- contracted and spread during sex (vaginal, oral, or anal) or skin-to-skin sexual contact. It can be difficult to determine when somebody first became infected with HPV as symptoms may develop years after a sexual encounter with an infected individual. HPV can be spread even when condoms are used and can be spread even in mutually monogamous relationships.
And because HPV resists desiccation (extreme dryness) and disinfection, it can survive for a long time on the surfaces of objects. As such, HPV can also be spread through non-sexual transmission, although it is not common.

5. Can HPV be passed from a mother to her child during pregnancy?

Though rare, HPV infection can pass through mother-to-child transmission when the infant passes through an infected birth canal.

6. What are all the health problems caused by HPV?

The main health problem caused by HPV is cervical cancer, the fourth most common cancer among women globally. Oncogenic HPV causes almost all cervical cancers, and a proportion of other oropharyngeal and anogenital cancers as well. High-risk types of HPV, such as HPV-16 and HPV-18, are the two types that most frequently cause cervical cancer.
HPV-16 and HPV-18 are additionally responsible for 85% of head and neck cancers and 87% of anal cancers, making these the second and third most frequently-related HPV cancers respectively. These two types can also cause cancers of the penis, the vulva, the vagina, and the oropharynx.
Other HPV-associated health problems for both men and women are mucosal infections and cutaneous infections. Mucosal HPV infections generally appear as oral lesions or genital warts that can develop on

the external genitalia, penis, vulva, and cervix. Many HPV types can cause anogenital warts, but in 90% of cases these anogenital warts are caused by HPV types 6 and 11.

7. Is there an immune response after natural HPV infection?

With some viruses, being infected once can protect against future exposure and reinfection. But for HPV It is unclear whether natural immunity develops after first infection. Only a fraction of the infections ever mounts an immune response, and antibodies are weak with low titers and low avidity. There is evidence that infection with one type of HPV may provide some protection against that one particular type, but it will not provide protection against other HPV types.

The infection is generally asymptomatic, and it is often not noticed by the infected individual. Most of the time, the immune system can clear away the virus on its own and does not cause significant health problems. But in certain cases of infection with high-risk types of HPV, cell growth can silently continue, largely undetected, until years later when it can develop into cancer.

Therefore, the HPV vaccine is an important cancer-prevention tool. The serological response after HPV vaccination is vastly stronger than the response after natural infection, providing people with strong, long-term immune protection to HPV.

8. What is the prevalence of HPV?

HPV is extremely common and an estimated 90% of people will be infected at some time in their lives, putting them at risk for serious health problems like cervical cancer in women. As of 2017, the World Health Organization estimates that worldwide prevalence of HPV in women is 11.7%. Latin America and the Caribbean have a prevalence of 16.1%, the second highest prevalence for women after Sub-Saharan Africa (24%).

The most common HPV types are types 16 and 18, and women who are infected with one type can also be infected with others at the same time.

Prevalence of HPV in men is high in all regions of the world and peaks at a slightly higher age than in women. Prevalence of any HPV type at the penis in particular is 18.7%; at the scrotum, 13.1%; and at the perineal region, 7.9%. Men who have at least 3 lifetime partners have 4.5 times the odds of contracting HPV of any type compared to men with fewer lifetime partners.

CERVICAL CANCER

9. What is the burden of cervical cancer?

Cervical cancer is the fourth most common cancer among women, with HPV-16 and HPV-18 accounting for over 70% of the world's cervical cancer cases. Globally, approximately 530,000 new cases of cervical cancer develop per year, and each year cervical cancer causes about 266,000 deaths. The World Health Organization has estimated that unless measures are taken to prevent and control cervical cancer, there will be about 700,000 new cases per year by 2030.

Persistent infection with a high-risk type of HPV is strongly associated with progression to cervical cancer. Important to note is that although HPV infection is the cause of more than 99% of cervical cancer cases, not every woman who is infected with HPV will get cervical cancer. These numbers vary by region, and lower-income regions are where the majority of cervical cancer cases occur (over 85%, or 445,000 cases per year). In these lower income regions, cervical cancer makes up almost 12% of all women's cancers, while in higher income regions cervical cancer makes up less than 1% of women's cancers. It is estimated that one in every 100 women in developing countries will have cervical cancer before the age of 75.

In the Americas, cancer is the second leading cause of death. In the region as a whole, cervical cancer is the fourth leading cause of death for women. However, in 11 countries in the region cervical cancer is the top cause of cancer death in women, and in 12 countries in the region it is the second cause of cancer death. An estimated 83,200 women in the Americas are newly diagnosed with cervical cancer each year, and each year 35,680 women die from the disease. Over half of these women (52%) are under 60 years old.

10. How long after an HPV infection does it take for cancer to develop in the body?

While most people who are infected with HPV do not develop cancer, persistent infection with a high-risk HPV type that is undetected or inadequately treated can progress to invasive carcinoma. When this happens, the time from infection to disease will usually take 10-20 years or longer, but it can sometimes take less time than that. Immunocompromised individuals, including those with HIV, are more likely to have persistent HPV infection and faster progression to cancer.

11. How does HPV infection progress to disease?

The progression to cervical cancer begins with normal epithelial cells becoming infected with HPV and ends with cervical cancer. Cervical cancer develops at the transformation zone, that corresponds to that area where the columnar epithelium is being replaced by squamous epithelium. During this process, glandular columnar cells changing into squamous cells are more prone for being infected with HPV. Then within months or years, persistent infections can cause the development of pre-malignant glandular or squamous intraepithelial lesions, and then to cancer.

However, 70-90% of HPV infections are asymptomatic, most infections clear spontaneously in 1-2 years, and most cervical lesions never progress to cancer. Mild lesions are common in the cervix, especially for women in their 20s and 30s. However, precancerous conditions, while not yet cancer, cause changes to cells that result in a higher probability of developing cancer, especially with persistent untreated infection with high-risk HPV types. The time from infection to cancer usually takes 10-20 years or longer, but it can take less time than that.

Pre-malignant lesions are histologically classified as cervical intraepithelial neoplasia (CIN) using the CIN classification system; or cytologically classified as squamous intraepithelial lesions (SIL), using the Bethesda System.

12. What is the difference between the histological classification system (CIN) and the cytological classification system (Bethesda System) for cervical cancer and pre-cancer?

There are many systems for classifying precancerous cervical conditions, based on cytology and histology. The most useful systems according to the WHO are the cervical intraepithelial neoplasia (CIN) classification system; and the Bethesda System. The International Classification of Diseases (ICD) references both systems of classification.

a) The cervical intraepithelial neoplasia (CIN) classification system: This system accounts for the different natural histories seen with different degrees of dysplasia. Although the CIN classification system is still used in many places for cytological reports, it should really only be used for histological reports (i.e., results of tissue sample examination via biopsy). Histological classification is used for diagnosis (as opposed to cytological classification, which is used for screening).
   i) Normal epithelium (no infection of HPV)
   ii) Atypia (some abnormal cells detected)
   iii) CIN1 (mild cervical dysplasia)
   iv) CIN2 (moderate to marked cervical dysplasia)
   v) CIN3 (severe cervical dysplasia to carcinoma in situ)
   vi) Invasive carcinoma (cervical cancer)

b) The Bethesda System: This system should only be used for cytological reports (i.e., results of smear examination via Pap smear). Unlike histological classification, cytological classification is used for screening and not diagnosis. Squamous intraepithelial lesions (SILs) describe abnormal changes in squamous cells (thin, flat cells on the outer surface of the cervix). Because it is difficult to distinguish CIN2 from CIN3 with cytological examination, the Bethesda System combines CIN2 and CIN3 into one group called high-grade squamous intraepithelial lesions (HSIL). CIN1 results are called low-grade squamous intraepithelial lesions (LSIL). Atypical cells are divided into ASCUS (atypical squamous cells of undetermined significance) and ASC-H (atypical squamous cells: cannot exclude a high-grade squamous intraepithelial lesion).

i) Normal epithelium (no infection of HPV)
ii) ASCUS or ASC-H (borderline, some abnormal cervical cells detected)
iii) LSIL (mild cervical dysplasia, cellular changes associated with HPV)
iv) HSIL (moderate to severe cervical dysplasia, combines CIN2 and CIN3)
v) Invasive carcinoma (cervical cancer)

CIN2/3 (HSIL) lesions have a higher likelihood of progressing to cancer than CIN1 (LSIL) lesions. It is possible to move between the grades and most CIN/SIL lesions spontaneously regress, but the higher grade the lesion is, the less probability it has of regressing than if it were a low-grade lesion. Please see below table for more information on cytological and histological terminology:

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13. How are HPV infection and cervical pre-cancer screened for?

HPV testing, cytology and visual inspection with acetic acid (VIA) are all recommended screening tests for cervical cancer. Screening is not done to diagnose disease, but to identify whether an individual has is at higher risk of having the disease or has a precursor to the disease.

a) HPV testing: HPV testing is the most effective tool for detecting cervical cancer risk. HPV testing detects HPV DNA (or RNA for one test) to identify the presence of high-risk HPV types, such as HPV-16 or HPV18.

   The sample can be either taken by the provider or self-collected by the woman in her own home. The Pan American Health Organization and the World Health Organization recommend that, when feasible, HPV testing should be done first as it has the best performance.

   HPV testing is not recommended for women under the age of 30, as HPV infection in young women is very common, usually resolves spontaneously on its own, and only a small percentage of persistent infections ever develop into pre-cancer. The exception to this recommendation is women and girls who are HIV-positive, as they are at much higher risk of developing cervical cancer.

b) Cytology: Cytology-based screening is the most commonly used screening method. It is used to assess whether epithelial cells are abnormal. Cervical or vaginal swabs are taken by a provider using a spatula and/or small brush. The samples are then either fixed onto slides and examined by a trained cytotechnician (i.e., conventional cytology, known as a pap smear or pap test); or they are immersed in a solution and sent to a laboratory to be examined by a trained cytotechnician (i.e., liquid-based cytology, or LBC). Cytology, while common, has a challenge of low-quality test results.

c) Visual inspection with acetic acid (VIA): VIA screening uses visual examination with the naked eye to identify lesions. During the procedure, a trained health care provider applies dilute (3-5%) acetic acid to the cervix and examines it for at least 1 minute to visualize changes in cervical cells. VIA is broadly used in low-resource settings as an inexpensive alternative to cytology-based screening and may be used alone or following an HPV test. VIA is often used alongside early treatment procedures.

14. How is cervical cancer diagnosed?

Diagnostic or confirmatory tests are used to help with the diagnosis of disease, since not all women with positive screening results actually have pre-cancer. The most commonly used cervical cancer diagnostic tests are colposcopy; biopsy; and endocervical curettage (ECC).

a) Colposcopy: Colposcopies are typically used to guide biopsies of any abnormal areas, and aid in determining whether cryotherapy or loop electrosurgical excision procedure (LEEP) is the most appropriate treatment. A colposcopy uses a colposcope, which is a microscope fitted with a light and used for examining the uterine cervix, to examine cellular patterns and surrounding blood vessels of the cervix, vagina, and vulva.
b) Biopsy: A biopsy is the removal of small samples of abnormal tissue to be examined under a microscope. It is used to determine the degree of abnormality of cell changes at the cervix and allows histological confirmation of lesions to rule in or out cervical cancer. Biopsies are often taken from areas of the cervix that are VIA-positive, or alternatively a colposcopy can be done to help identify the site where a biopsy should be taken in cases where the lesion is not visible using VIA.
c) Endocervical curettage (ECC): ECC is a simple procedure in which surface cells are gently scraped from the endocervical canal and then sent to a laboratory for evaluation. If a provider suspects pre-cancer or cancer, ECC might be used to examine cells in an area of the cervix not visible using VIA or colposcopy.

15. What means the “screen-and-treat” approach?

Low--resource regions usually opt to use a “screen-and-treat” approach rather than a “screen, diagnose and treat” approach. In “screen-and-treat” approach, treatment decisions depend on the results of the screening test alone; if the screening is positive, treatment is provided immediately (i.e., without a diagnostic test). Diagnostic tests are not always recommended, as they can be a major drain on resources and hold a high risk for false-positive and false-negative results.

16. How are HPV infection and cervical pre-cancer treated?

There is no specific treatment for infection with the virus itself, but there is treatment of pre-cancer, - which is very effective in preventing the progression of HPV to cervical cancer. Precancerous lesions can be treated using ablative methods or via surgical removal of tissue. The three treatment methods for cervical pre-cancer are cryotherapy, loop electrosurgical excision procedure (LEEP), and cold knife conization (CKC).

a) Cryotherapy: Cryotherapy is the burning or freezing of abnormal tissue. It is fast, simple, and does not require anesthesia or electricity. This makes it the most common treatment method for low-income countries. During the procedure, a highly cooled metal disk is applied to the cervix to freeze and subsequently destroy precancerous lesions, after which the frozen area regenerates to normal epithelium. To be eligible for cryotherapy, the lesion must not be suspicious for invasive cancer; it must have a

positive screening or be histologically CIN2+; and it must not extend to the endocervical canal or beyond the area of the cryoprobe. Training for the procedure takes a few days, and the procedure can be performed by trained physicians or non-physicians in an outpatient setting. Women who undergo cryotherapy should be warned that they will likely experience profuse, watery discharge for up to one month.

b) Loop electrosurgical excision procedure (LEEP): When the lesion is large, or when a person is not eligible for cryotherapy, surgical removal of tissue is the necessary course of action. One surgical method is LEEP, which removes the lesion and the entire transformation zone. This both treats the pre-cancer and produces a specimen for pathological examination so that invasive cancer can be ruled out. During the procedure, an electrosurgical-powered tool made from thin wire forms a loop to cut abnormal areas away from the cervix. LEEP requires electricity, local anesthesia, and extensive training to perform; but it takes only about 10-15 minutes and may be performed in an outpatient setting by a trained provider.

c) Cold knife conization (CKC): CKC is reserved for the most serious and recurrent cervical lesions, when the case cannot be resolved by cryotherapy or LEEP. A cone-shaped area is removed from the cervix, including parts of the outer and inner cervix. This tissue is sent to the pathology laboratory to diagnose or rule out invasive cancer, and to make sure all abnormal tissue has been entirely removed. A CKC is performed in a hospital by gynecologists or surgeons trained to perform CKC and manage bleeding and other complications. It requires general or regional anesthesia and cervical healing takes about 4-6 weeks.

17. How can HPV and cervical cancer be prevented?

The best way to prevent cervical cancer is for girls aged 9-14 years to be vaccinated, before they start sexual activity, and for women to get screened. PAHO/WHO recommend that women between the ages of 30 to 49 years be screened for cervical cancer. These screening tests detect early pre-cancerous changes in the cervix, which can then be treated safely before cervical cancer has any chance to develop. If the test is negative, it is still advisable to follow up with a repeat screening. -

HPV VACCINATION

18. What vaccines are available to prevent HPV?

There are three vaccines currently on the market that can be used to prevent high-risk HPV types: the bivalent vaccine, Cervarix; the quadrivalent vaccine, Gardasil; and the nonavalent vaccine, Gardasil 9. In the Region as of 2018, the PAHO Revolving Fund offers the bivalent and the quadrivalent vaccines. WHO Strategic Advisory Group of Experts (SAGE) and the PAHO Technical Advisory Group on Immunization (TAG) recommend that the HPV vaccine be given to girls aged 9-14 years. This is because the vaccine does not cure existing infection, so it must be given before girls become sexually active. Make sure the patient receives all recommended doses of the vaccine.

The **Revolving Fund** of the Pan American Health Organization (**PAHO**) is a cooperation mechanism for the joint procurement of vaccines, and other supplies what facilitates the countries in the Americas to pool their national resources and obtain vaccines at their lowest price, thereby allowing Member States to stay protected vaccine-preventable diseases such as cervical cancer. (Click HERE to read more about the PAHO Revolving Fund.)

All three vaccines have been rigorously tested for safety and efficacy, and none contain live agents or viral DNA, so they are non-infectious and non-oncogenic. Each protects against the most common carcinogenic HPV types (16 and 18). Administration is recommended before the age of sexual debut for all three vaccines, as the vaccine should predate papillomavirus infection whenever possible. Below is a table summarizing the main characteristics of each vaccine:

	Bivalent 2vHPV (Cervarix)	Quadrivalent 4vHPV (Gardasil)	Nonavalent 9vHPV (Gardasil 9)
HPV types included	HPV types 16 and 18	HPV types 6, 11, 16, 18	HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58
Manufacturer	GlaxoSmithKline	Merck	Merck
Year of license	2007	2006	2014
Adjuvant	-Made in insect cells -500µg aluminum hydroxide + 500µg 3-O-desacyl-4-monophosphoryl lipid A (AS04)	-Made in yeast -225µg Amorphous aluminium hydroxyphosphate sulphate (AAHS)	-Made in yeast -500µg AAHS adjuvant
L1 protein types contained in each 0.5mL dose	20µg HPV-16; 20µg HPV-18	20µg HPV-6; 40µg HPV-11; 40µg HPV-16; 20µg HPV-18	30µg HPV-6; 40µg HPV-11; 60µg HPV-16; 40µg HPV-18; 20µg HPV-31; 20µg HPV-33; 20µg HPV 45; 20µg HPV-52; 2-µg HPV-58;
Mode of delivery	Intramuscular injection		
Storage	-Stored at 2 - 8 °C (36 - 46 °F) -Must *never* be frozen -Protected from light, stored in original packaging, administered immediately after removal from refrigerator, and never used past expiration date		
Target Age	9-14 years old	9-14 years; up to 26 years	9-14 years; up to age 26 for girls and up to age 21 for boys
Target Gender	Females (limited data on efficacy in males)	Females and Males	Females and Males
Dose Schedule	-Age 9-14: 2 doses (0.5 mL at 0 and 6 months) -Age ≥15: 3 doses (0.5 mL at 0, 1-2, 6 months)		
Maximum Interval between doses	There is no maximum recommended interval between doses. However, an interval no longer than 12-15 months is suggested in order to complete the schedule promptly and before becoming sexually active.		

Source: Human papillomavirus vaccines: WHO position paper May 2017

19. What are the HPV vaccines composed of?

All of the vaccines are subunit vaccines, meaning that they do not contain live parts of the viral antigen, but only the antigenic components which are essential for the body to build a strong immune response against HPV. The major component forming the basis of the vaccine is called a Virus-Like Particle, or VLP. VLPs are biological cages that contain the protective protein shell (capsid) of a virus, but not the virus itself. The major capsid protein used to develop the HPV vaccine is called L1, grown in insect or yeast cells. L1 assembles itself into empty VLPs, effectively mimicking the human papillomavirus and signaling the immune system to begin producing neutralizing antibodies. But while these VLPs appear structurally indistinguishable from HPV itself, they contain no DNA, they are noninfectious, and they have a very low

risk of adverse reactions. They are therefore considered very safe, and they induce strong immune responses that protect against HPV infection and disease.

20. What is the immune response to the HPV vaccine?

After natural infection, only 70-80% of women develop serum antibodies to HPV, and the degree of protection is low. After vaccination, however, the serological response is much stronger (1-4 logs higher) than that of natural infection. The mechanism of protection is likely mediated by polyclonal neutralizing antibodies against the L1 surface protein, which have better affinity and avidity. One likely reason that this immune response to vaccination is so much higher than natural infection is the route of immunization. Natural infection is entirely intraepithelial, so antigens have little access to the lymphatics and draining lymph nodes where immune responses start. But the HPV vaccine, like most VLP vaccines, is administered intramuscularly and this greatly enhances immunogenicity. Intramuscular deltoid injection gives immediate access to lymph nodes, rapidly activating Helper T cell and B cell responses. Additionally, VLPs are inherently highly immunogenic due to the repeating L1 capsomer pattern that triggers the innate immune sensors and leads to strong adaptive immunity. Long-term HPV-specific antibody persistence is a result of long-lived plasma cells in the bone marrow, which regularly produce IgG antibodies.
Immune responses are highest in 9 to 11-year-old girls prior to sexual debut, and high coverage in girls (>80%) provides herd protection for boys. Even with lower antibody titers the HPV vaccine continues to provide protection, and there is no evidence that the vaccine response wanes over time.

21. Who should get the HPV vaccine?

According to SAGE and TAG recommendations, the primary target population for vaccination is girls aged 9-14 years before they become sexually active. Girls are a prioritized population in order to prevent cervical cancer. Secondary target populations are girls ≥15 years, or males. These populations should only be vaccinated if doing so does not take away resources from vaccination of the primary target population, or from cervical cancer screening programs.
The currently available vaccines are licensed for use by the manufacturers in girls and women aged 9 to 26 and boys and men aged 9-21 (if male vaccination is included in the country's national immunization program). If indicated by the national immunization program, any teenage girls and boys who did not start or finish the HPV vaccine series should be vaccinated now. Men who have sex with men, transgender individuals, and immunocompromised and/or HIV-positive individuals should all be vaccinated up until age 26 if they did not receive the vaccine when they were younger.

22. Why is it important for girls to be vaccinated against HPV?

HPV is an extremely common virus that causes cervical cancer-- one of the top killers of women in the world. However, when the vaccine is given to girls at a young age before exposure to the virus, it can protect them from the most harmful types of HPV.

23. What is the recommended schedule for HPV vaccines?

The schedule for HPV vaccination is determined by the recipient's age at first dose. PAHO/WHO currently recommends a 2-dose schedule with at least 6 months between doses (manufacturer recommendations cite a 6-month interval between doses for the bivalent and quadrivalent vaccines, and a 5-month interval between doses for the nonavalent vaccine). This 2-dose schedule is generally appropriate for those aged 9-14. Those receiving the *second dose* at the age of 15 or older are still covered by the 2 doses, provided the *first dose* was given before age 15. A 3-dose schedule should be used for those receiving the *first dose* at age 15 years or older (0, 1-2, 6 months). Those who are immunocompromised and/or HIV-infected, even if under the age of 15, should also be given the 3-dose schedule. And while there is no maximum interval between doses, an interval no longer than 12-15 months is recommended to maximize chances of the individual receiving both doses before becoming sexually active.

24. Why is it recommended to wait 6 months between the doses of the vaccine?

This spacing is very important as the HPV vaccine may be less effective if doses are given too close together, and sufficient interval between doses provides longer-lasting immunity. Memory B cell responses are activated after the first dose of the vaccine and take at least 4-6 months to mature into high-affinity B cells. The interval between doses reactivates these high-affinity B cells and kick starts their differentiation into antibody-secreting plasma cells. This 6-month gap allows the body to develop long-term immunity, whereas with shorter dose gaps between doses, affinity maturation may not occur, and protection duration may be shorter.

25. Are the HPV vaccines efficacious and effective in preventing cervical cancer?

The HPV vaccines are highly efficacious and effective in preventing cervical cancer, and large-scale studies and ongoing surveillance have demonstrated that efficacy and effectiveness are comparably high for all three vaccines.

All the HPV vaccines were licensed owing to extensive evidence displaying high clinical efficacy in young women and, for the quadrivalent and nonavalent vaccines, also in young men. Efficacy has been found to be over 90% for the prevention of persistent infection with HPV types 16 and 18-- the two most common carcinogenic types. The quadrivalent and nonavalent vaccines also contain HPV types 6 and 11, which are responsible for anogenital warts. Both of these vaccines have displayed close to 100% protection for HPV-naive individuals in the prevention of anogenital warts associated with HPV types 6 and 11; and about 83% efficacy for all anogenital warts regardless of HPV type. For all young women regardless of prior HPV exposure, vaccination offers 62% efficacy against anogenital warts.

Effectiveness has likewise been found to be similar for all three licensed HPV vaccines in preventing cervical cancer. At the population level, HPV vaccination has offered powerful herd protection, and vaccination programs have witnessed significant reductions in the prevalence of high-risk HPV types and high-grade cervical abnormalities that can lead to cervical cancer, which generates considerable long-term reductions in HPV infection and diseases in the unvaccinated population. These herd effects are expected even when coverage is as low as 40%. Moreover, when vaccination coverage is over 80% in girls, countries with female-only vaccination programs will still witness large reductions in HPV infection and diseases in unvaccinated young men.

Because the HPV vaccine is designed to be preventative and can only prevent infection and disease *before* exposure, it is not as effective or efficacious in preventing cervical cancer with previous exposure to one or more HPV type. The HPV vaccine does not treat existing HPV infection or disease. Therefore, it is very important that girls be vaccinated young, before the initiation of sexual activity, when their chances of HPV exposure are lower.

26. Can the HPV vaccine be co-administered with other vaccines?

HPV vaccines can be co-administered with other non-live and live vaccines, and indeed this is recommended as giving multiple vaccines in a single visit improves the probability that girls will get all necessary vaccines on schedule. Ample evidence reveals non-inferiority of antibody response and no increase in adverse events for the co-administration of the HPV vaccine with other vaccines.

If the HPV vaccine is administered at the same time as other injectable vaccines, it should be given at different injection sites using separate syringes.

27. Can the HPV vaccines be used interchangeably with one another?

There is limited evidence concerning the safety and efficacy of the HPV vaccines when used interchangeably with one another. These three vaccines are comparable in terms of immunogenicity for the prevention of cervical cancers, but the three vaccines contain different components and indications. As such, every effort should be made to use the same vaccine for every dose. If the vaccine used for previous doses is unavailable or unknown, however, it is acceptable to use any of the HPV vaccines to complete the scheduled doses.

28. How should the HPV vaccine be stored?

All three HPV vaccines should be kept at 2 to 8 °C (36 to 46 °F) and should be administered to the patient as soon as they are removed from the refrigerator. The vaccines should never be frozen, and if vaccines are exposed to freezing temperatures the vaccine manufacturers and/or the local immunization program should be contacted. The vaccines must be protected from light, should be stored in their original packaging, and they should never be used past the expiration date printed on the label.

HPV VACCINE SAFETY

29. Are the HPV vaccines safe?

The HPV vaccines are extremely safe. All three HPV vaccines were tested on tens of thousands of people before they were licensed, with no evidence of serious adverse events.
After a vaccine is licensed, its safety continues to be monitored rigorously in every country where it is introduced. Millions of doses of HPV vaccines have been administered worldwide, and post-marketing study data has revealed that the vaccines are well-tolerated and very safe with no reason for any major safety concerns. Adverse reactions are not significantly different from those observed with other vaccines, and major adverse events are extremely rare. Most reports of adverse events are local pain/soreness or redness in the injection site, fever, nausea and headache. In almost all cases these side effects resolve quickly on their own. Many people experiencing no adverse events at all.

Health professionals play an essential role in teaching their patients that HPV vaccines are safe and prevent a deadly cancer, and convincing parents and adolescents of the need to receive the HPV vaccine.

30. Who monitors the safety of the HPV vaccine?

Most of the countries in the Region are monitoring post-licensure HPV safety using a system to report and investigate Events Supposedly Attributable to Vaccination or Immunization (ESAVIs). An ESAVI is a symptom or signal that arises after receiving a vaccine, which *may or may not be* related to the vaccination itself. ESAVIs do not necessarily imply a cause-effect relationship between the reaction and the vaccine, and when identifying ESAVIs, an investigation must be done to determine whether a clinical symptom is a direct result of vaccination.

The Global Advisory Committee on Vaccine Safety (GACVS) is a committee that gives independent scientific advice to WHO on issues concerning global or regional vaccine safety concerns and gives national immunization program recommendations based on these concerns. GACVS has repeatedly and rigorously monitored the safety of the HPV vaccines for since its introduction. The committee has found no evidence of any significant safety concerns among the many millions of patients who have received the HPV vaccine, and no evidence that the vaccine leads to any increase in the onset of chronic diseases or autoimmune diseases in any population.

31. Are there any ESAVIs thought to be associated with the HPV vaccine?

Just like any medicine, adverse events can sometimes occur that may be associated with vaccination. The most commonly reported ESAVIs are local pain/soreness or redness at the injection site and headache. Mild ESAVIs include fever, nausea and dizziness, though this generally resolves freely on its own. Most people experience no adverse events at all.

In extremely rare cases (approximately 1.7 cases per million doses), anaphylaxis can occur, and must be treated immediately if suspected. Any person who experiences a serious adverse event, such as anaphylaxis, after any dose of the vaccine should not receive additional doses. Similarly, people who have serious allergies to any component of the vaccine should not be given the vaccine.

Some people may experience fainting spells (post-vaccination syncope). This is common in adolescents after any injection and sitting or lying down can help dizziness subside. It is recommended that healthcare workers and vaccine administrators ask their patients to sit during vaccination and remain seated and observed for 15 minutes following administration of the vaccine. Any vaccine recipient who faints after vaccination should be checked to ensure that the fainting is not a result of another disease.

32. Is the vaccine safe for people who are immunocompromised and/or infected with HIV?

The vaccine can be used safely in individuals who are immunocompromised (whether by disease or by medication) and/or individuals who are HIV-infected, and they should receive 3 doses no matter if <15 years old at the first dose. However, there is limited data on the immunogenicity of the vaccine in immunocompromised and/or HIV-infected population.

33. Is the vaccine safe for women who are currently pregnant?

Because there have not been extensive studies on HPV vaccination during pregnancy, the vaccine is not recommended for pregnant women. However, the available data indicate that the vaccine will not cause harm to the mother or the fetus if it is inadvertently given to a woman who is pregnant. If a woman becomes pregnant after she has started her series of HPV vaccines, she should delay the next dose(s) until the pregnancy is completed. It is safe for both mother and child if she receives the HPV vaccine while breastfeeding.

34. Should a woman who is infected with HPV still get the HPV vaccine?

The vaccine's role is to prevent viral infection before it occurs. It is not recommended to test for HPV before administering the vaccine, but even if a woman is tested and found to be infected with HPV, she should still be given the vaccine if she is the appropriate age to receive it. There are many types of HPV, and even if a woman is infected with one type the vaccine can still protect her from other types she has not yet been exposed to, including high-risk cancer-causing or genital wart-causing types.

35. Is there anyone who should not get the HPV vaccine?

The HPV vaccine should not be given to any person who has had an anaphylactic reaction after a prior HPV dose, or to an ingredient contained in the vaccine. Pregnant women should avoid receiving the HPV vaccine, as there is limited data on vaccine safety during pregnancy.

HPV VACCINE EDUCATION AND PROGRAMMATIC CONCERNS

36. Do boys get vaccinated for HPV?

The HPV vaccines are licensed for use in both female and male populations based on excellent safety and efficacy profiles. However, as HPV vaccination offers women direct protection from cervical cancer, any effective cervical cancer prevention program must prioritize girls first. The WHO therefore recommends that the primary target population for HPV vaccination programs should be girls aged 9-14 years, prior to sexual debut, and males should be considered a secondary target population. Gender-neutral vaccination is only recommended if it is affordable and does not drain resources from the primary target population or from cervical cancer screening programs.

37. Should vaccinated women receive cervical cancer screening?

HPV vaccination, while it is an extremely important primary prevention strategy to prevent cervical cancer and other diseases caused by HPV, does not abolish the necessity of cervical cancer screenings. WHO recommends that all women should be screened for cervical cancer at least once from the ages of 30-49, regardless of vaccination status, as the vaccine does not protect against all high-risk types of HPV. A comprehensive cervical cancer-prevention strategy should therefore include both HPV vaccination and cervical cancer screenings.

38. What are the considerations that affect a country or territory's choice of which vaccine to use in their national immunization program?

The current evidence indicates that the three vaccines are comparable in terms of their immunogenicity for the prevention of cervical cancer, so which HPV vaccine to use is dependent on other factors. This includes (but is not limited to) the burden of HPV and its associated disease outcomes; the price of the vaccines; vaccine approval; and programmatic considerations.
Cost-effectiveness plays a large role. Cost-considerations for countries and territories include the vaccine price per-dose; operational costs; prevalence of HPV; uptake of cancer screening and treatment; and available resources. Evidence points to the cost-effectiveness of vaccinating pre-adolescent girls,

especially in resource-limited settings. In the Region of the Americas, the Revolving Fund of the Pan American Health Organization supports countries obtain vaccines at a lower price. PAHO's Revolving Fund offer the bivalent and the quadrivalent vaccines to the Region.

39. As a health care provider, what is my role and responsibility in the prevention of cervical cancer?

Health workers play an important role in the prevention of cervical cancer by reaching people in their communities and vaccinating the most vulnerable children in the most difficult-to-access areas. Health workers are also essential in providing screening and treatment of HPV-related infections and continued cervical cancer screening. *They remind girls and their families to receive all doses of the vaccine needed* to be fully protective, they aid girls' attendance at vaccine sites.
Health workers also have essential roles as educators. People turn to their health care providers to learn about the information and services available to them, and direct communication between providers and patients is the best way to influence health seeking behaviors. Health workers also communicate with local health managers, community leaders, religious leaders, local authorities, school administrators, and parents. Health workers raise awareness about the availability of the HPV vaccine and provide accurate information that counteracts misinformation and myths. They educate communities about the importance of vaccination for preventing cervical cancer; and about reducing risky behaviors that may lead to HPV infection, cervical cancer, and other associated diseases. They educate women and adolescents about screening, diagnosis, and treatment of cancer and precancerous lesions.
They play an essential role by maintaining detailed records on information such as the number of individuals vaccinated; each recipient's age; and the dosage given to each recipient.

HPV VACCINE AND CERVICAL CANCER MYTHS AND MISCONCEPTIONS

40. If a child is too young to be having sex, why should that child be vaccinated for a disease that is sexually-transmitted?

Children who are vaccinated young, ideally *before* sexual activity, mount a higher immune response to the vaccine than those who are vaccinated older, or vaccinated after exposure to HPV (the highest immune responses are seen in girls aged 9-14 years before first sexual activity). This means that the

vaccine provides them with better protection during their life, for many years after receiving the vaccine. Studies indicate strong protection from disease for up to 10 years after vaccination, with no evidence that vaccine efficacy decreases over time.

41. Does the HPV vaccine promote sex initiation?

The HPV vaccine does not promote sex initiation, but it protects of developing a serious and dangerous disease.

42. Has HPV vaccination been linked to Guillain-Barré syndrome, or any other syndrome or disease?

The Global Advisory Committee on Vaccine Safety (GACVS) - collected large population-level country data on the following safety concerns: Bell's palsy, Complex Regional Pain Syndrome (CRPS), Postural Orthostatic Tachycardia Syndrome (POTS), premature ovarian insufficiency, primary ovarian failure, and venous thromboembolism. They found no evidence of causal association between the HPV vaccine and any of these conditions.

43. Are cervical cancer screening tests painful? Is part of the cervix or womb removed?

No, cervical cancer screenings are painless, though there may be slight discomfort during pelvic examination.

44. Does an abnormal screening test mean that the patient has cancer?

An abnormal screening test does not mean that the woman has cervical cancer. A positive screening means that early changes in the cervix, such as lesions, have been detected, which *may* lead to cancer over time if not treated.

FINAL KEY TAKEAWAYS

45. What are the essential messages that I should know and convey to patients and the general community about cervical cancer and the HPV vaccine?

Information concerning local vaccination, screening and treatment locations must be given, as well as information that complies with the country's national guidelines. This includes information about the specified target populations, such as age ranges for vaccination of girls; age ranges for cervical cancer screening of women; and whether vaccination is indicated for girls only, or for both girls and boys. The following box presents the key messages that are *universal for any setting* and must be emphasized:

KEY MESSAGES FOR HPV VACCINATION AND CERVICAL CANCER PREVENTION

a) **Cervical cancer is one of the leading causes of death for women, and it is caused by the human papillomavirus (HPV). Most people will become infected with HPV during their lifetime.**
b) **There is a safe and effective vaccine that can protect people against high-risk HPV types .**
c) **The HPV vaccine works best if it is given before the start of sexual activity.**
d) **Follow-up appointments are necessary to ensure that all required HPV vaccine doses are administered.**
e) **The HPV vaccine cannot treat or cure existing HPV infection. Nonetheless, girls who are already sexually active should still be given the vaccine if they are within the recommended age group.**
f) **There are tests that can detect pre-cancer in the cervix, these lesions can be treated before they develop into cervical cancer.**
g) **All women aged 30-49 years should be screened for cervical cancer at least once.**

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