

# Chapter 4: HPV Vaccination

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Comprehensive Cervical Cancer  
Control: A guide to essential practice  
(C4 GEP)

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# Contents

KEY POINTS.....	3
ABOUT THIS CHAPTER.....	3
ROLE OF THE HEALTH CARE PROVIDER.....	3
HPV VACCINES.....	4
Vaccine protective effect.....	5
Vaccine Safety.....	5
Vaccine Administration and Schedule .....	6
Characteristics of HPV Vaccines.....	7
TARGET POPULATION .....	8
DELIVERY STRATEGIES.....	9
Health Facility-based.....	9
School-based.....	9
Outreach .....	10
Integrated services.....	11
COMMUNITY MOBILIZATION.....	11
OBTAINING CONSENT/ASSENT FOR A GIRL TO GET VACCINATED .....	11
ADDITIONAL RESOURCES .....	13
FREQUENTLY ASKED QUESTIONS.....	14
PRACTICE SHEET 1: Vaccine characteristics and the cold chain .....	17
PRACTICE SHEET 2: Injection safety.....	19
PRACTICE SHEET 3: The immunization session.....	20
PRACTICE SHEET 4: Data collection.....	22
SAMPLE FORM 1: SAMPLE REPORT FORM FOR ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI) ..	25
SAMPLE FORM 2. REPORTING OF NATIONAL HPV VACCINE COVERAGE FOR THE WHO-UNICEF JOINT REPORTING FORM .....	27
SAMPLE FORM 3: SAMPLE TALLY SHEET FROM WHO GUIDANCE DOCUMENT ON HOW TO RECORD NUMBER OF HPV DOSES GIVEN ON SINGLE VACCINATION DAY ON HPV VACCINE COVERAGE MONITORING .....	28
SAMPLE FORM 4. SAMPLE HPV VACCINE SERVICE PROVIDER LOG BOOK FROM WHO GUIDANCE DOCUMENT ON HPV VACCINE COVERAGE MONITORING.....	30

## KEY POINTS

- There are now vaccines that prevent the precursors of cervical cancer.
- The majority of HPV-associated cancers worldwide are caused by only two HPV types: HPV 16 and 18. HPV 16 and 18 cause about 70% of cervical cancer in all regions of the world.
- Currently, two prophylactic vaccines against HPV 16 and 18 are licensed in most countries. HPV vaccination can be added to a comprehensive cervical cancer prevention strategy as a primary prevention tool.
- Both HPV vaccines have an excellent safety profile and can be co-administered with other vaccines.
- The primary target population for HPV vaccination is girls before initiation of sexual activity. The recommended target ages for HPV vaccination is 9-13 years.
- Completion of all doses at the specified intervals is recommended.
- The vaccines cannot treat HPV infection or HPV-associated disease.
- HPV vaccination does not replace cervical cancer screening.
- HPV vaccination is safe and immunogenic in HIV-infected individuals. There are no contraindications to vaccinating HIV-infected persons with HPV vaccine.
- One of the two current vaccines also protects against HPV types that cause anogenital warts.

## ABOUT THIS CHAPTER

This chapter provides information on HPV vaccination. It describes the types of vaccines, the outcomes that could be prevented by the vaccines, the target population for the vaccines, and how to organize vaccination sessions and administer the vaccine.

## ROLE OF THE HEALTH CARE PROVIDER

Because of the many unique features of HPV vaccines, including the target population of 9-13 year old girls, health care providers can play an important role beyond administering the vaccines: they can be a source of information to girls who are eligible for the vaccine, parents, teachers, health care professionals, policy makers, and the general community.

HPV vaccine implementation should include educating girls about the benefit of vaccination, and can provide opportunities to educate their mothers about the need for cervical cancer screening and early treatment. HPV vaccine introduction may also provide the impetus to improve, strengthen, and integrate health services for 9-13 year olds at national, regional, and local levels. For example, health care providers could facilitate adolescent access to other health services for 9-13 year olds. Community

health worker networks may be mobilized to assist adolescents to access various services, and vaccine introduction may also serve as an opportunity to improve and facilitate adolescent health education.

The role of the vaccine provider includes: link with the role of the teacher and other school officials

- Education
  - Educate girls and their parents about HPV vaccine and cervical cancer
  - Counsel girls to complete the three-dose series
  - Educate the community about cervical cancer prevention
- Vaccine management and delivery
  - Determine eligibility (age, grade/class, pregnancy status, allergies)
  - Safely administer vaccine to eligible girls
  - Ensure appropriate management of vaccines, supplies, and waste management.
- Provide training and education to teachers and other school officials to educate girls and to facilitate vaccination sessions where school-based delivery is implemented.
- Record keeping and reporting
  - Record information on girls who are vaccinated, including name, date of birth or age, and date, type of vaccine and dose number received
  - Maintain tally sheets for regular data collection and reporting
  - Manage and report adverse events following immunization (AEFI)

## HPV VACCINES

Two HPV vaccines are currently available worldwide: a bivalent vaccine, against HPV types 16 and 18 (these two types cause 70% of cervical cancers in most of the world) and a quadrivalent vaccine, against HPV 16 and 18 as well as HPV 6 and 11 (6 and 11 are responsible for benign anogenital warts and recurrent respiratory papillomatosis, a disease where recurrent growths occur in the airways, frequently on the vocal cords). Neither vaccine contains a live virus; therefore, they don't act by causing an infection. Both vaccines are prophylactic (prevent HPV infections) and are most effective when administered prior to infection with HPV, which is acquired by most individuals shortly after sexual debut. The vaccines are not therapeutic (cannot be used to treat existing HPV and HPV-related disease), nor do they have any effect on progression to disease (precancer and cancer) in persons who have HPV infection at the time of vaccination.

## **Vaccine protective effect**

Data from several large clinical trials of HPV vaccines have demonstrated very high efficacy of both vaccines against initial and persistent infection with the HPV types in the vaccines and associated conditions in young women aged 15-26 years who had not been exposed to the HPV types targeted by the vaccine.

At the planned end of the vaccine trials for both vaccines, HPV 16- or 18-related cervical intraepithelial neoplasia grade 2 and 3 (precancer) and adenocarcinoma in situ were measured. These cervical precancerous lesions are used as proxy for cervical cancer. Trial results indicate very high efficacy for protection against these cervical lesions in women who were DNA negative in the cervix and did not have antibodies in their blood stream for HPV 16 and 18 at the time of vaccination.

Clinical trials of the quadrivalent vaccine also measured genital warts as a primary endpoint. As with cervical lesions, the trial results showed high efficacy of the quadrivalent HPV vaccine against genital warts (also called condyloma) in those who were proven not infected with HPV 16 and 18 by serum and cervical tests at the time of vaccination.

Antibody to HPV 16 and 18 studies were conducted for both vaccines in girls aged 9-15 years. Results from the studies indicate that over 99% of vaccinated women developed antibodies after vaccination, and that antibody titres were higher in the girls who were 9-15 years old compared to those who were 16-26 years old.

There are on-going studies to determine the exact duration of HPV vaccine protection. However, it is reassuring that there has been no evidence of waning immunity nine years after vaccination in women who were vaccinated as part of the clinical trials in the early 2000s. Booster doses are not currently recommended. There is preliminary evidence of cross-protection (protection against infections caused by other disease-associated HPV types that are not included in the current vaccines), and the extent and duration of protection is under study.

## **Vaccine Safety**

### **Evidence to date**

Safety studies of both HPV vaccines were conducted in thousands of women around the world prior to licensure. Results of the studies demonstrated that both vaccines were well tolerated with no major safety concerns for either vaccine. Post-licensure, the most common adverse events reported in vaccinated girls in the United States have involved injection site pain and swelling. Similar post-marketing surveillance from other countries including Australia, United Kingdom, Malaysia, Italy, and Netherlands has not identified any new health risks other than mild adverse events such as fever, dizziness, and nausea. In the United States, syncope (fainting) has been reported after HPV

vaccine administration. Syncope can occur after any medical procedure and is not uncommon in adolescents following receipt of any vaccine. It is recommended that adolescents should be seated during HPV vaccine administration, and observed for 15 minutes afterwards to avoid possible fainting.

### **Precautions and contraindications**

HPV vaccine should not be given to people who have experienced severe allergic reactions after a previous vaccine dose or to a component (e.g., yeast) of the vaccine.

HPV vaccines are not recommended for use in pregnancy. If a girl becomes pregnant after initiating the vaccination series, the remainder of the regimen should be delayed until after completion of the pregnancy. In the event that the HPV vaccine is inadvertently administered to a girl who is pregnant, no intervention is necessary.

Although HPV vaccines are recommended in young girls before onset of sexual activity, available data do not indicate any safety concerns if the quadrivalent vaccine is administered while a girl is lactating. There are no published results from studies on the bivalent vaccine.

HPV vaccination of boys and men for prevention of cervical cancer is not recommended as a strategy at this time because it is not as cost-effective in for reduction of cervical cancer as vaccinating 70% or more of target aged young girls.

### **Vaccine Administration and Schedule**

This paragraph refers to WHO current recommendations, for the latest WHO recommendation on the HPV vaccine schedule are found at:

[http://www.who.int/immunization/policy/immunization\\_tables/en/](http://www.who.int/immunization/policy/immunization_tables/en/).

Both vaccines are administered in a schedule of currently 3 doses within 6 months. The dose for each vaccine is administered intramuscularly using 0.5 mL of liquid suspension. For the quadrivalent vaccine, the second dose is given 2 months after the first dose, and the last (third) is given 6 months after the first dose. For the bivalent vaccine, the second dose is administered 1 month after the first, and the third dose at 6 months after the initial dose.

A minimum interval of 4 weeks between the first and second doses, and a minimum interval between the second and third doses of 12 weeks is recommended for the quadrivalent vaccine. If flexibility in the schedule is necessary for the bivalent vaccine, the manufacturer recommends that the second dose is administered between 1 and 2.5 months after the first dose. Re-starting is not necessary if the series is interrupted, but remaining doses should be administered as close to the recommended intervals as possible.

Studies are currently ongoing to assess alternative HPV vaccine schedules, both with respect to the interval between doses and the number of doses. Although a few countries such as Mexico, Colombia, Switzerland, and parts of Canada, are currently using alternative dosing schedules, this is not approved or recommended by WHO at this time. WHO monitors the availability of new data to determine when global recommendations should be updated.

Every effort should be made to administer the same vaccine for all three doses since the two products have different characteristics and components. In addition, data are lacking on the safety, immunogenicity or efficacy of the two vaccines when used interchangeably. However, if the vaccine used for prior doses is unknown or unavailable, either of the marketed HPV vaccines can be administered to complete the schedule.

Administering more than one recommended vaccine together at a single visit increases the likelihood that vaccines will be received on schedule. HPV vaccines are non-infectious and can be administered at the same time as other non-live vaccines. Studies show that the following combinations of co-administration are safe and do not reduce the immune response in the following:

- The quadrivalent HPV vaccine with a recombinant hepatitis B vaccine
- The quadrivalent HPV vaccine with the combined diphtheria / tetanus / pertussis / poliomyelitis vaccine
- The bivalent vaccine with the combined diphtheria / tetanus / pertussis / poliomyelitis vaccine

Guidance will be updated as results of ongoing co-administration studies become available.

### Characteristics of HPV Vaccines

Attributes	Quadrivalent	Bivalent
Comercial name (Manufacturer)	Gardasil/Silgard (Merck)	Cervarix (GlaxoSmithKline)
HPV VLP types in vaccine	6,11,16,18	16,18
Disease protection	Cervical cancer Genital warts	Cervical cancer
Number of doses	3	3
Dosing interval	0, 2, and 6 months	0, 1, and 6 months
Presentation	1 dose vial	1 and 2 dose vials
Method of administration	Intramuscular injection	Intramuscular injection
Contraindication	Severe allergic reaction to any	Severe allergic reaction to any

	vaccine component after first dose, or allergy to yeast	vaccine component after first dose, or allergy to latex
Coadministration with other adolescent vaccines	hepatitis B diphtheria/tetanus/pertussis/poliomyelitis	diphtheria/tetanus/pertussis/poliomyelitis
Shelf life	36 months at 2-8° C	48 months at 2-8° C for 1 dose vial 36 months at 2-8° C for 2 dose vial

## TARGET POPULATION

HPV vaccination is most effective when administered prior to infection with HPV types in the vaccine. WHO recommends routine vaccination of girls 9-13 years of age because they are not as likely to have begun sexual activity. The target age span may vary in different settings, and should be determined at the country level based on expected sexual debut for most girls in that country and the feasibility of reaching most girls in that target age. Some countries have used a grade/class approach in selecting eligible girls, where a single grade/class is vaccinated irrespective of the age of the girls. However, the vaccines are currently not recommended in girls younger than 9 years of age.

Depending on resources and need, when the vaccine is introduced for the first time, countries may also consider time-limited catch-up vaccination of cohorts of girls who are older than the target age group but who may still benefit from vaccination (i.e. they are presumed to not yet be HPV infected).

Because HPV vaccines are non-infectious, they can be administered safely to persons who are immunocompromised as a result of medications or diseases such as HIV/AIDS. However, the immune response and vaccine efficacy might be less than that in persons who are immunocompetent.

### Recommended Target Population

Women/girls:

- Ages 9-13 years
- Before onset of sexual activity

Who should NOT receive HPV vaccine:

- Pregnant women/girls
- Girls younger than 9 years of age
- Persons with a life-threatening allergy to any component of the vaccine



## DELIVERY STRATEGIES

Introduction of any new vaccine requires addressing many logistical and programmatic issues. Implementation of HPV vaccines presents the additional challenges of delivering three doses of vaccine over a six-month period to a new target age group of girls aged 9-13 years. Thus, HPV vaccine implementation may require use of unique and innovative vaccine delivery strategies.

The ideal HPV vaccine delivery strategies, as outlined in the WHO position paper, should be:

- Compatible with existing vaccine delivery infrastructure and cold-chain capacity
- Affordable, cost-effective, and sustainable
- Able to achieve the highest possible coverage

The WHO HPV vaccine position paper further recommends prioritizing strategies that reach girls who are least likely to have access to cervical cancer screening later in life, as well as approaches that would provide opportunities for integration with other health services for adolescents.

In practice, however, no single delivery strategy is able to include every desirable characteristic described above, and countries may need to consider trade-offs between strategies that maximize coverage and those that are most feasible, affordable, and sustainable. Ultimately, a combination of strategies may be needed to achieve high coverage, while optimizing resources to prevent disruption of other services.

Delivery strategies include:

### Health Facility-based

This method provides opportunities for all eligible girls to receive the HPV vaccination in a fixed health care facility. This strategy reduces transport and personnel costs (such as travel allowance) to the health system because it relies on the girls to come to the health facility. Demonstration projects in several countries have shown that it is possible to achieve high HPV vaccine coverage through offering vaccination in health centres.

Delivering vaccines through health centres is most effective in areas where the majority of girls live in close proximity to the clinics, such as in urban communities.

### School-based

A promising strategy that has been used successfully in some developing countries is school-based vaccination. If feasible, school-based HPV vaccination can serve as an opportunity to create or strengthen school health services and improve health education and communication. However, this delivery strategy is resource-intensive and may not

be efficient in settings where school enrollment and attendance is low for the target aged girls.

A school-based strategy may determine eligibility of girls for vaccination either by age of the individual girl, or vaccinate all girls in the given grades in which the majority of the target age group are enrolled.

Teachers and other school officials can have an instrumental role in the successful delivery of HPV vaccines in their schools. Teachers can educate students and their parents about the benefits of vaccination for the eligible population, dispel rumors and myths around the vaccine, and answer other questions and concerns prior to vaccination day. On the day of the vaccination, school staff can assist the vaccine delivery team to ensure eligible girls are vaccinated, identify eligible girls who are absent on that day, and facilitate other logistical issues as appropriate.

Since school-based vaccination will not provide all eligible girls with an opportunity to get the HPV vaccine, either because they are not enrolled or because of absenteeism, this strategy must be supplemented by strategies to reach girls who are not in school in order to ensure equitable access to the vaccine. Of note, teachers can play the important role of identifying girls who are not in school and motivate them to get the vaccine.

## Outreach

In countries where a large proportion of the population lives in areas with limited access to health services, an outreach delivery strategy may be appropriate to ensure equitable vaccination opportunities for all adolescent girls. For HPV vaccination, a minimum of three outreach sessions would be needed within a six-month period.

In the context of vaccine delivery, outreach strategy refers to any strategy that requires health care workers to leave their usual facility to transport and deliver immunization services in a variety of fixed or mobile sites. Some examples of outreach venues are community centres, school buildings, and youth/adolescent centres. Outreach can be done on a regular or scheduled basis or irregularly such as a mop-up outreach.

Another possible outreach strategy, taking into account that many target-aged girls live in poor, distant and isolated communities and no longer attend school, is to train community workers (if permitted by national guidelines) to:

- Transport and maintain a cold-chain thermos with sufficient vaccines for 9-13 year old girls who have not received the HPV vaccines
- Administer the vaccines to those girls who fit eligibility criteria
- Record vaccinations in standardized forms

Notes: Training community workers to counsel, determine lack of contraindications and administer injections safely and correctly has been successfully implemented with provision of Depo-provera, syndromic treatment of childhood pneumonias and other preventive programmes.

### **Integrated services**

Packaging HPV vaccination with other interventions, for example, with deworming treatment or with insecticide treated bednets (ITNs), or concurrent administration with other vaccines such as recombinant Hepatitis B with the quadrivalent vaccine or diphtheria-tetanus-acellular pertussis-inactivated poliovirus with the bivalent vaccine, may promote sharing resources and knowledge across programmes, optimize costs and logistics, and serve to integrate a variety of services in a more efficient and effective way.

Some delivery strategies, such as outreach and other mobile delivery strategies, are particularly conducive to combining HPV vaccination with other adolescent health services.

### **COMMUNITY MOBILIZATION**

The success of HPV vaccine delivery depends on high community awareness through information, education, communication activities as well as counseling with parents, if needed. Quantitative and qualitative assessment of knowledge, attitudes, and beliefs about HPV vaccines can help identify barriers and sensitivities such as fear of adverse effects and misconceptions regarding infertility that need to be addressed prior to vaccine introduction. A vaccine against a sexually transmitted infection that is recommended only for girls can be confusing to parents and may lead to unnecessary reluctance to vaccinate daughters at an age when they are most likely to benefit from the vaccine.

Involvement of a broad range of governmental and non-governmental stakeholders throughout a community can facilitate introduction and implementation of HPV vaccines. School-based vaccination will require coordination between the Ministries of Health (MOH) and Education (MOE), and the collaboration of school officials at district, regional and local levels (for more information see Chapter 3).

### **OBTAINING CONSENT/ASSENT FOR A GIRL TO GET VACCINATED**

How consent for vaccination needs to be obtained is determined in national laws and regulations. In general, informed consent requires the health worker to appropriately and fully inform the patient of the risks and benefits of the vaccination. Most vaccinations are given to children who because of their age cannot yet legally consent.

Therefore, parents provide “parental consent” for their children to be vaccinated. For vaccination in early childhood, i.e., between 0 and 5 years of age, parental consent can be implied when a parent voluntarily brings the child to be vaccinated at a health clinic.

In the case of HPV vaccination, the target group of girls between 9 and 13 years old may come in for vaccination without a parent present (for example, during school-based vaccination delivery). Carrying out the parental consent process will still be required in most countries based on the established legal age of consent for vaccination. At a minimum, this will include informing the parents of the planned vaccination and depending on the country regulations, providing a parent with the possibility for the child to opt out of the procedure.

Some health authorities may require explicit written consent to be obtained from parents. This will have planning, logistical and resource implications and may introduce new challenges for the vaccination implementation that will need careful planning.

While only parents in most countries can legally provide consent for the vaccination, the girl receiving the HPV vaccination will also need to be informed of the risk and benefits of the vaccination. In addition, when vaccination is not mandatory, she has to voluntarily participate in the vaccination, thus providing “assent” to the treatment.

Situations may arise in which the girl expresses the wish to be vaccinated while parent explicitly do not consent or this consent cannot be produced. In this situation, an additional consideration is to take account of the best interest of the child. In such a case, best international standards require the health worker to assess the “competence” of the girl, i.e., she demonstrates she understand the benefits, risks and consequences of the treatment versus no-treatment and is capable of making this decision for herself. Such alternative mechanisms are important, especially for marginalized and disadvantaged girls such as those orphaned by HIV, whose access to the HPV vaccine would likely to be affected by parental consent requirement.

## ADDITIONAL RESOURCES

WHO Human papillomavirus (HPV) resources

<http://www.who.int/nuvi/hpv/resources/en/index.html>

Comprehensive guide to policy and decision-making. Includes links to HPV disease burden, key WHO documents on HPV vaccine, guidance on HPV vaccine introduction, and HPV vaccine characteristics and safety. Examples of information that can be found are:

- HPV disease burden by country
- Cervical cancer incidence and mortality worldwide
- WHO position paper on HPV vaccines
- Key points on HPV vaccines for policy-makers and health professionals
- HPV vaccine safety
- HPV vaccine programme guidance
- WHO Cervical Cancer Prevention and Control Costing Tool (C4P Tool) information
- WHO School Vaccination Programme Readiness Assessment Tool
- Resources from other organizations

[http://www.who.int/immunization\\_financing/tools/cmyp/en/index.html](http://www.who.int/immunization_financing/tools/cmyp/en/index.html)

Link to guidelines for developing a comprehensive Multi-Year Plan (cMYP) for immunization to support countries in improving their planning for immunization.

[http://www.who.int/vaccine\\_safety/initiative/tools/HPV\\_Vaccine\\_rates\\_information\\_sheet.pdf](http://www.who.int/vaccine_safety/initiative/tools/HPV_Vaccine_rates_information_sheet.pdf)

## FREQUENTLY ASKED QUESTIONS

### **Why are HPV vaccines needed?**

Certain human papillomavirus (HPV) types cause cancer, including: cervical, vulvar, vaginal, penile, anal, and oropharyngeal (base of the tongue, tonsils and back of throat) cancers. Certain HPV types also cause most cases of genital warts.

HPV is a common virus that is easily spread by skin-to-skin contact during sexual activity with another person. It is possible to have HPV without knowing it, so it is possible to unknowingly spread HPV to another person.

HPV vaccine is a strong tool in prevention. These safe, effective vaccines are available to protect against HPV types 16 and 18 that cause approximately 70% of cervical cancers worldwide.

### **How common are the health problems caused by HPV?**

HPV is the main cause of cervical cancer, the 2nd most common cancer in women in the developing world. Of the 275,000 women who die every year from cervical cancer, over 85% live in developing countries.

### **What HPV vaccines are currently available?**

Two HPV vaccines are currently available worldwide. As of 2012, HPV vaccine has been introduced into the national immunization program in over 40 countries. These vaccines are Cervarix (made by GlaxoSmithKline) and Gardasil (made by Merck).

### **How are the two HPV vaccines similar?**

Both vaccines are very effective against diseases caused by HPV types 16 and 18; HPV 16 and 18 cause most cervical cancers, as well as other HPV associated cancers.

Both vaccines have been shown to prevent cervical precancers in women.

Both vaccines are very safe.

Both vaccines are non-infectious and cannot cause disease.

Both vaccines are given as shots and require three doses.

### **How are the two HPV vaccines different?**

The vaccines have different adjuvants—a substance that is added to the vaccine to increase the body's immune response.

Only one of the vaccines (Gardasil) protects against HPV types 6 and 11, the types that cause most genital warts in females and males.

### **Who should get HPV vaccine?**

The target population for HPV vaccination is girls who are 9-13 years old. The vaccines are not recommended in girls younger than 9 years of age.

### **Why is HPV vaccine recommended at ages 9-13 years old?**

For the HPV vaccine to work best, it is very important for preteens to get all three doses (shots) long before any sexual activity with another person begins. It is possible to be infected with HPV the very first time that a person has sexual contact with another person. Also, the vaccine produces higher antibody levels when given at this age compared to older ages.

### **What is the recommended schedule (or timing) of the three HPV doses (shots)?**

Three doses (shots) are recommended over six months.

### **Are the HPV vaccines safe and effective?**

Most national regulatory agencies, including the Food and Drug Administration in the U.S.A. and the European Medicines Agency, have licensed the vaccines and note them to be safe and effective. Both vaccines have been administered to millions of girls and women around the world without serious side effects. Common, mild side effects included pain where the shot was given, fever, headache, and nausea. As with all vaccines, the safety of these vaccines is monitored very carefully. Ongoing vaccine safety studies continue to show that HPV vaccines are safe.

### **Can HPV vaccines treat HPV infections or cervical cancer?**

HPV vaccines will not treat or get rid of existing HPV infections. In addition, HPV vaccines do not treat or cure health problems (like cancer or warts) caused by an HPV infection that occurred before vaccination. It is important for adult women to still get cervical cancer screening even if they have completed the HPV vaccine series.

### **How important is it to get HPV vaccine?**

The HPV vaccines are important tools to prevent cervical cancer caused by HPV types targeted by the vaccine.

### **Should pregnant women be vaccinated?**

HPV vaccines are not recommended for use in pregnant women. However, studies have shown neither vaccine caused problems for babies born to women who got the HPV vaccine while they were pregnant. Getting the HPV vaccine when pregnant is not a reason to consider ending a pregnancy. But, to be on the safe side until more is known, a pregnant woman should not get any doses of either HPV vaccine until her pregnancy is completed.

### **What should a woman do if she realizes she received HPV vaccination while pregnant?**

If a woman realizes that she got any shots of an HPV vaccine while pregnant, she should wait until after her pregnancy to finish the remaining HPV vaccine doses.

### **Can women with HIV infection be vaccinated?**

Studies show that HPV vaccination is safe and immunogenic and does not cause problems for HIV-infected women who got the vaccine. HPV vaccine is not contraindicated in HIV-infected women.

### **Can boys get vaccinated?**

HPV vaccines are currently not recommended by WHO for administration to boys for prevention of cervical cancer because high vaccine coverage (>70%) in the primary target population of 9-13 year old girls is more cost-effective in reducing cervical cancer than including boys.

### **Do people faint after getting HPV vaccines?**

People faint for many reasons. Some preteens and teen may faint after any medical procedure, including receiving vaccines. It is possible for falls and injuries to occur after fainting. Sitting or lying down for about 15 minutes after a vaccination can help prevent fainting and related injuries.



## **PRACTICE SHEET 1: Vaccine characteristics and the cold chain**

### **Dosing schedule**

Both vaccines are administered in three doses over a six-month time frame. For the quadrivalent vaccine, the second dose is given 2 months after the first dose, and the last (third) is given 6 months after the first dose. For the bivalent vaccine, the second dose is administered 1 month after the first dose, and the third dose at 6 months after the initial dose.

### **Formulation**

Both HPV vaccines are available as turbid white suspensions for intramuscular injection. When stored, they may separate into a white deposit and a clear colourless supernatant and should be shaken before use.

### **Presentations**

The single dose vial of Gardasil vaccine is prequalified<sup>1</sup> by WHO. Each vial contains a 0.5 ml suspension. Gardasil does not contain any preservatives or antibiotics, and vials can be ordered in pack sizes of 1, 10, and 100.

Cervarix is available in two WHO pre-qualified presentations. The single dose vial has a rubber butyl stopper and contains a 0.5 ml suspension without any preservatives or antibiotics. The two-dose presentation contains a 1.0 ml suspension without preservatives or antibiotics. The vials can be ordered in pack sizes of 1, 10, and 100.

Both vaccines should be administered as soon as possible after being removed from the refrigerator. Opened vials of the product should be discarded at the end of the immunization session or after six hours, whichever comes first.

Both vaccines are also available as a pre-filled syringe; however, this presentation is not pre-qualified by WHO.

### **Storage and cold chain**

All formulations of HPV vaccine should be refrigerated at +2 to +8 degrees Celsius. HPV vaccines are exceptionally sensitive to temperatures lower than +2 and lose

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<sup>1</sup> WHO Prequalification of vaccines: WHO provides a service to UNICEF and other UN agencies that purchase vaccines, with regards to the acceptability, in principle, of vaccines from different sources for supply to these agencies. For detailed information see:

[http://www.who.int/immunization\\_standards/vaccine\\_quality/pg\\_system/en/index.html](http://www.who.int/immunization_standards/vaccine_quality/pg_system/en/index.html)

efficacy if frozen. Therefore, HPV vaccine cannot be placed in or near the freezer portion of the refrigerator nor directly on a frozen ice pack. If the refrigerator is a side-opening model, the vaccines should not be stored in the door as the temperature is more likely to fluctuate when opening and closing the refrigerator. The temperature of the refrigerator should be monitored and adjusted as necessary to maintain the appropriate temperature. This can be done by checking the thermometer regularly (minimum twice daily) and by keeping a freeze tag in the refrigerator to detect episodes of freezing temperatures. If a large supply of HPV vaccine is suspected to have been frozen or exposed to sub-zero temperatures, a shake test should be performed to determine whether the vaccine can be used or not.

<http://www.who.int/bulletin/volumes/88/8/08-056879/en/index.html> and Shake and Tell (article video 22 minutes) <http://vimeo.com/8381355> and Step by Step Shake Test (instructional video 10 minutes) <http://vimeo.com/8389435>.

If transport of vaccine is required, ice packs should be used to maintain a cold chain at +2 to +8 degrees Celsius. Frozen icepacks should be kept at room temperature for 5-10 or more minutes until the ice inside the ice packs can be heard to move when shaken before placing the vaccines in them. This is called "conditioning" the ice packs and prevents the vaccine from freezing when it is placed near the packs.

Both vaccines are sensitive to light and should be stored in the original box until ready to use.

### **Shelf life**

According to the package inserts, the shelf life is 3 years for 1-dose vials of Gardasil (link) and 4 years for 1-dose vials of Cervarix ([http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/000721/WC500024632.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000721/WC500024632.pdf))

### **Interchangeability**

There is no data on the interchangeability of the vaccines and every effort should be made to use the same vaccine for all three doses. However, if the vaccine used for prior doses is unknown or unavailable, either of the marketed HPV vaccines can be administered to complete the schedule.

## PRACTICE SHEET 2: Injection safety

WHO defines a safe injection as one that:

- Does not harm the recipient
- Does not expose the health care worker to any avoidable risks
- Does not result in waste that is dangerous to the community

Injection safety can be improved by following the practices below:

1. Always follow manufacturer recommendations for use, storage, and handling
2. Wash hands with soap and water and drip dry
3. Prepare injections in a clean designated area where blood and body fluid is unlikely
4. Prepare each dose immediately before administering. Do not prepare several syringes in advance
5. To minimize risk of injury, prepare work area such that:
  - a. The vaccine administrator is placed between the girl and needles and sharp objects
  - b. Monitoring tools and safety boxes are easily accessible
  - c. Each vaccinator has a designated safety box and can see the entrance hole when discarding needle
  - d. There is no need to set the needle down or move elsewhere to discard needle
6. Check the vial for condition and expiry date. Do not use if packaging is punctured, torn, or damaged, or if vial contains particles or if there is discoloration
7. Use a new auto-disable (AD) syringe for each girl
8. Do not touch any part of the needle
9. Never leave the needle in the top of the vaccine vial
10. Clean the injection site and inject entire content of the syringe into the deltoid muscle of the upper arm using a perpendicular 90 degree angle
11. Discard the syringe and needle in a safety box immediately after administering the vaccine; (a safety box should be a water-proof and tamper-proof container that is securely closed with only a small hole at the top large enough for syringe and needle to go through)
12. Do not recap the used needle and syringe
13. Do not overfill the safety box. Close the container and seal the opening when the box is  $\frac{3}{4}$  full
14. Keep safety boxes in a dry, safe place until they are safely disposed of
15. Do not dispose of used syringe and needles in an open box or container

### PRACTICE SHEET 3: The immunization session

Ensure the following are available:

1. Vaccine and syringes
2. IEC materials (e.g. flyers, pamphlets, posters)
3. Chair and table
4. Water and soap or hand sanitizer for cleaning hands
5. Trays and kidney dishes
6. Safety boxes with closed lid
7. Containers for used vials
8. Drugs to manage allergic reactions
9. Place to rest for 15 minutes after vaccination
10. Vaccination logbook (register)
11. Tally sheets
12. Personal vaccination cards
13. Calendar

Note: a pre-visit may be required if a school-based strategy is implemented

Before administering vaccine, the health care provider should determine that the girl is eligible for HPV vaccination, that the girl understands what is about to be done, and that she can refuse to be vaccinated.

1. Greet the girl (and parent if present)
2. Explain the purpose and benefits of HPV vaccination
3. Discuss potential risks and side-effects of vaccination
4. Discuss risks of not receiving the vaccine
5. Ask the girl (and/or her parent if present) if she has any questions and answer them clearly, using the minimum amount of technical terminology
6. Check that the girl understands the answer and correct any misunderstanding
7. Collect written consent of parent if applicable
8. Verify eligibility by checking that the girl:
  - a. Is within the target age
  - b. Is not pregnant
  - c. Is not allergic to any component of the vaccine
9. Determine which HPV vaccine dose will be administered during this session
10. Ask to see her vaccination card (or adolescent health card) if available to verify

11. Document the following information in vaccination logbook (register) and on vaccination card if available:
- a. Name of girl
  - b. Address
  - c. Date of birth and age (if unknown, determine age based on educated guess and document)
  - d. Date of vaccination
  - e. HPV dose number (1,2, or 3)
  - f. Date of previous doses if applicable

### **Administering the vaccine**

1. Make sure girl is in a seated position to minimize risk of syncope (i.e. fainting)
2. Check expiry date on the vial
3. Check the vaccine vial monitor (VVM)
4. Hold the vial between the thumb and middle finger and check condition. Do not use if packaging is punctured, torn, or damaged, or if vial contains particles or if there is discoloration
5. Mix the vaccine suspension by shaking the vial until the liquid is white and cloudy
6. Open the AD syringe package and remove the syringe and needle from package
7. Take off the needle cap without touching any part of the needle
8. Insert the needle into the vaccine vial and bring the tip of the needle to the lowest part of the bottom of the vial
9. Draw the entire contents of the vial into the 0.5 mL syringe until you notice a "click"
10. Inject entire content of the syringe into the deltoid muscle of the upper arm using a perpendicular 90 degree angle
11. Place a swab on the injection site and ask the girl to hold firmly. Do not massage the injection site
12. Discard the syringe and needle in the safety box immediately after administration
13. Determine due date for next vaccine dose and record on vaccination card
14. Remind her that she must receive 3 doses and the date for her next scheduled vaccination
15. Indicate date of next dose on vaccination card
16. Return updated vaccination card to the girl and ask her to bring it back on her next scheduled vaccination
17. Observe the girl for 15 minutes after administration in case of syncope
18. Should an adverse event occur, manage and document any adverse reaction

## PRACTICE SHEET 4: Data collection

### Monitoring vaccine coverage and program evaluation

Calculating HPV vaccine coverage is necessary for monitoring the performance of a vaccine programme, as well as for evaluating the impact of vaccine on a population.

Since HPV vaccination is recommended as a three-dose series of vaccines administered over a six-month period to adolescent girls with ages ranging from 9-13 years, monitoring will require collection of coverage data by dose and by year of age. At a minimum, the girl's date of birth or age, date of vaccine administration, and dose number should be recorded each time a vaccine is administered.

A standardized HPV Vaccination Coverage Monitoring Tool is available with instructions and standardized forms and tables (link). Below is a brief summary of the contents and instructions.

Data collection and reporting tools for vaccine providers:

- Personal immunization (adolescent health) cards
- Vaccine provider logbook (one for each delivery site)
- Tally sheet (one for each vaccination session)
- Monthly record sheet of vaccination days (one per delivery site)

Data collection and reporting tools for supervisors:

- Service Delivery Site Monthly Summary Table for each calendar year

Data collection and reporting tools for district health offices:

- District Health Office Monthly Summary Table for each calendar year
- District Health Office Annual Reporting form

Data summary and reporting tools for national health office:

- National Health Office Monthly Summary Table
- National Health Office Annual Reporting form

Data collection procedure:

1. Use one logbook (register) per delivery site
2. Register each girl by collecting the following information
  - a. Name

- b. Address
- c. Date of birth and reported age (Note: if neither is known, vaccinator should document an age based on educated guess)
- d. Date of vaccination
- e. HPV dose number (1,2, or 3)
- f. Date of previous doses if applicable
- g. Age at previous doses if applicable
- 3. Ask girl if she is pregnant
- 4. Ask girl to present her personal vaccination card. Check the logbook (register) to verify which dose is being given. If she doesn't have her card, check the logbook using her personal information
- 5. Register each administered dose by marking through one zero in the appropriate box (based on age and dose number) on the standard tally form
- 6. At the end of the vaccination day, tally number of HPV doses given, by dose number and by age
  - a. Count and record number of strike-throughs on tally form for each dose number and age category
  - b. If sub-total is zero, record the number 0 with a strike-through

### **Monitoring adverse events following immunization (AEFIs)**

An AEFI can be described as an adverse clinical event that is temporally related to vaccination but that may or may not be caused by the vaccine or the vaccine process. AEFIs can range from minor events such as a mild reaction at the injection site to life-threatening events including anaphylaxis and possibly death. Although an AEFI can be caused by the vaccine itself, reported AEFIs are more commonly either a coincident event that is not related to the vaccine but due to programmatic / human errors that compromise the vaccine quality, or allergic reactions to components in the vaccine.

Monitoring HPV vaccine safety is of particular importance because it is a new vaccine and is administered to an age group not previously targeted for vaccination in many countries. In addition, there has been some controversy surrounding a vaccine for prevention of a sexually transmitted infection. Groups opposed to vaccines for any reason may initiate or perpetuate rumors of vaccine safety and spurious associations with coincident adverse events to discourage HPV vaccination in the population. Because misinformation can be detrimental to vaccine acceptability and vaccination efforts, a robust AEFI monitoring infrastructure is essential to dispel rumors and demonstrate continued safety of HPV vaccines.

AEFIs can be classified into five categories:

1. Vaccine reaction

- Caused or precipitated by inherent properties of vaccine
- 2. Programme error
  - Caused by error in preparation, handling, or administration of vaccine
- 3. Coincidental
  - Event that happens after vaccination but is not necessarily caused by the vaccine or related to vaccination
- 4. Injection reaction
  - Caused by anxiety of or pain from the act of injection rather than the vaccine
- 5. Unknown
  - Cause cannot be determined

Common HPV vaccine reactions (resolve spontaneously, rarely require treatment):

- Redness, pain, swelling, or induration at injection site
- Fever
- Headache, myalgia, arthralgia
- Nausea, vomiting, diarrhea, abdominal pain
- Pruritis, rash, urticaria
- Syncope

Serious adverse events are extremely rare. Anaphylaxis can be causally related to HPV vaccination and precautions should be taken to avoid vaccinating girls with previous allergic reactions to vaccine components. If anaphylaxis is suspected, the girl should be observed and immediately treated as needed.

### **AEFI reporting**

A system should be in place to facilitate prompt reporting and investigation of AEFIs. National regulatory authorities and national immunization technical advisory groups (NITAG) should take a proactive role in investigating reports of serious adverse events to verify that there is no link to HPV vaccine and develop communication messages to address rumors.

All suspected AEFIs should be immediately reported to health authorities using a standard AEFI reporting form (Annex 1). Serious events such as death, hospitalization, or geographic cluster of AEFIs should be rapidly investigated (within 48 hours).



## SAMPLE FORM 1: SAMPLE REPORT FORM FOR ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

### Demographic details

Family name:				First name:		Identification number:	
Address:				Date of birth (DD/MM/YY) ____/____/____ or, Age: ____ Years ____ Months			
Region:		District:		Sex: ____ Male ____ Female			
Health facility (or vaccination centre):				Reporter (health worker):			
Vaccine(s) given*	Route	Site of injection	Lot number of vaccine	Lot number of diluent	Manufacturer**	Expiry date of vaccine	Expiry date of diluent

\*If event follows routine vaccination, give name and dose number e.g., measles1, DPT-2, OPV-2.

\*\*Include information for diluent if applicable.

Date vaccinated	Date AEFI started	Onset interval	Date of report
<b>Tick box(es) and describe event(s):</b>			
<input type="checkbox"/> Severe local reaction: >3 days ____, beyond nearest joint <input type="checkbox"/> or hospitalized ____ <input type="checkbox"/> Abscess: sterile ____ or bacterial ____ <input type="checkbox"/> Sepsis <input type="checkbox"/> Toxic shock syndrome		<input type="checkbox"/> Anaphylactic reaction <input type="checkbox"/> Anaphylaxis <input type="checkbox"/> Seizures, including febrile seizures <input type="checkbox"/> Encephalopathy <input type="checkbox"/> Thrombocytopenia	
<input type="checkbox"/> Other AEFI (describe; use additional sheet if needed):			
<b>Outcome:</b> <input type="checkbox"/> Recovered fully <input type="checkbox"/> Recovered partially <input type="checkbox"/> Unknown <input type="checkbox"/> Hospitalized    Date of admission (DD/MM/YY) ____/____/____    Date of discharge (DD/MM/YY) ____/____/____ <input type="checkbox"/> Died:    Date of death (DD/MM/YY) ____/____/____			

**Past medical history (including history of similar reaction or other allergies) and any other relevant information(e.g., other cases).** Use additional sheet if needed. :

*Province (or District) Level Office to complete:*

<b>Date report received:</b> (DD/MM/YY) ____/____/____	<b>Checked by:</b>
<b>Investigation needed?</b> ____Yes ____No	<b>If yes, date investigation started:</b> DD/MM/YY)____/____/____
<b>Investigator:</b>	<b>AEFI Investigation ID:</b>
<b>Causality assessment:</b>	<b>Certainty:</b>

*This form to be completed by health worker and returned to the immunization program manager or appropriate local health authority (or as per established reporting system in country).*

## SAMPLE FORM 2. REPORTING OF NATIONAL HPV VACCINE COVERAGE FOR THE WHO-UNICEF JOINT REPORTING FORM

### HPV Vaccine Doses administered: 2010

[\(Table instructions\)](#)

	Females			
	Vaccine administered (age in years)	A. 1st dose	B. 2d dose	C. 3d dose
4220	9			
4230	10			
4240	11			
4250	12			
4260	13			
4270	14			
4280	15+			
4290	unknown age			

[http://www.who.int/immunization\\_monitoring/routine/joint\\_reporting/en/index.html](http://www.who.int/immunization_monitoring/routine/joint_reporting/en/index.html)

### SAMPLE FORM 3: SAMPLE TALLY SHEET FROM WHO GUIDANCE DOCUMENT ON HOW TO RECORD NUMBER OF HPV DOSES GIVEN ON SINGLE VACCINATION DAY ON HPV VACCINE COVERAGE MONITORING

Date of vaccination ...../...../.....	District: _____ Town/village: _____ Vaccination site: _____			
Age (years)	No. of HPV1 doses given	No. of HPV2 doses given	No. of HPV3 doses given	OPTIONAL (sum up rows)
9	00000 00000 00000 00000 00000	00000 00000 00000 00000 00000	00000 00000 00000 00000 00000	
	00000 00000 00000 00000 00000	00000 00000 00000 00000 00000	00000 00000 00000 00000 00000	
	Subtotal 9yrHPV1=	9yrHPV2=	9yrHPV3=	=
10	00000 00000 00000 00000 00000	00000 00000 00000 00000 00000	00000 00000 00000 00000 00000	
	00000 00000 00000 00000 00000	00000 00000 00000 00000 00000	00000 00000 00000 00000 00000	
	10yrHPV1=	10yrHPV2=	10yrHPV3=	=
11	00000 00000 00000 00000 00000	00000 00000 00000 00000 00000	00000 00000 00000 00000 00000	
	00000 00000 00000 00000 00000	00000 00000 00000 00000 00000	00000 00000 00000 00000 00000	
	11yrHPV1=	11yrHPV2=	11yrHPV3=	=
12	00000 00000 00000 00000 00000	00000 00000 00000 00000 00000	00000 00000 00000 00000 00000	
	00000 00000 00000 00000 00000	00000 00000 00000 00000 00000	00000 00000 00000 00000 00000	
	12yrHPV1=	12yrHPV2=	12yrHPV3=	=
13	00000 00000 00000 00000 00000	00000 00000 00000 00000 00000	00000 00000 00000 00000 00000	

	00000 00000 00000 00000 00000	00000 00000 00000 00000 00000	00000 00000 00000 00000 00000	
	13yrHPV1=	13yrHPV2=	13yrHPV3=	=
14	00000 00000 00000 00000 00000 00000 00000 00000 00000 00000	00000 00000 00000 00000 00000 00000 00000 00000 00000 00000	00000 00000 00000 00000 00000 00000 00000 00000 00000 00000	
	14yrHPV1=	14yrHPV2=	14yrHPV3=	=
$\geq 15$	00000 00000 00000 00000 00000 00000 00000 00000 00000 00000	00000 00000 00000 00000 00000 00000 00000 00000 00000 00000	00000 00000 00000 00000 00000 00000 00000 00000 00000 00000	
	$\geq 15$ yrHPV1=	$\geq 15$ yrHPV2=	$\geq 15$ yrHPV3=	=
Unknown	00000 00000 00000 00000 00000 00000 00000 00000 00000 00000	00000 00000 00000 00000 00000 00000 00000 00000 00000 00000	00000 00000 00000 00000 00000 00000 00000 00000 00000 00000	
	UnkHPV1=	UnkHPV2=	UnkHPV3=	=
	Total of HPV1 doses given =	Total of HPV2 doses given =	Total of HPV3 doses given =	Grand total =

## SAMPLE FORM 4. SAMPLE HPV VACCINE SERVICE PROVIDER LOG BOOK FROM WHO GUIDANCE DOCUMENT ON HPV VACCINE COVERAGE MONITORING

District: _____ Town/Village: _____ Service delivery site: _____									
Name	Address	DOB (dd/mm/yyyy)	HPV1		HPV2		HPV3		Comments
			Date Given (dd/mm/yyyy)	Age of girl (years)	Date Given (dd/mm/yyyy)	Age of girl (years)	Date Given (dd/mm/yyyy)	Age of girl (years)	