INTRODUCING

HPV VACCINE

INTO NATIONAL IMMUNIZATION PROGRAMMES

Guide to
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Guide to Introducing HPV Vaccine into National Immunization Programmes


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Guide to

INTRODUCING

HPV VACCINE

INTO NATIONAL IMMUNIZATION PROGRAMMES
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AD syringe</td>
<td>Auto-disable syringe</td>
</tr>
<tr>
<td>AEFI</td>
<td>Adverse event following immunization</td>
</tr>
<tr>
<td>cMYP</td>
<td>Comprehensive multi-year plan</td>
</tr>
<tr>
<td>CTC</td>
<td>Controlled Temperature Chain</td>
</tr>
<tr>
<td>EPI</td>
<td>Expanded Programme on Immunization</td>
</tr>
<tr>
<td>EVM</td>
<td>Effective vaccine management</td>
</tr>
<tr>
<td>GACVS</td>
<td>Global Advisory Committee on Vaccine Safety</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HPV</td>
<td>Human papillomavirus</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
</tr>
<tr>
<td>ICC</td>
<td>Inter-agency coordinating committee</td>
</tr>
<tr>
<td>IEC</td>
<td>Information, education and communication</td>
</tr>
<tr>
<td>MOH</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>NITAG</td>
<td>National immunization technical advisory group</td>
</tr>
<tr>
<td>SAGE</td>
<td>Strategic advisory group of experts on immunization</td>
</tr>
<tr>
<td>UNESCO</td>
<td>United Nations Education, Scientific and Cultural Organization</td>
</tr>
<tr>
<td>UNFPA</td>
<td>United Nations Population Fund</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
</tr>
<tr>
<td>VLP</td>
<td>Virus-like particle</td>
</tr>
<tr>
<td>VVM</td>
<td>Vaccine vial monitor</td>
</tr>
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<td>WHO</td>
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ABOUT THIS GUIDE

This document is intended for use by national immunization programme managers and immunization partners involved in providing implementation support to countries.

General guidance about planning the introduction of a vaccine into a national immunization programme is provided in the document *Principles and considerations for adding a vaccine to a national immunization programme: from decision to implementation and monitoring* published by the World Health Organization (WHO) in 2014 and available at [http://www.who.int/immunization/programmes_systems/policies_strategies/vaccine_intro_resources/nvi_guidelines/en/](http://www.who.int/immunization/programmes_systems/policies_strategies/vaccine_intro_resources/nvi_guidelines/en/).

The specific objectives of this guide are:
- To inform the policy discussions and operational aspects for the introduction of HPV vaccine into a national immunization programme.
- To provide up-to-date references on the global policy, as well as the technical and strategic issues related to the introduction of HPV vaccine into a national immunization programme.

Globally, there is almost a decade of HPV vaccine introduction experience from dozens of countries across all income groups. WHO has compiled these lessons and their implications for action in a companion document entitled *Scaling Up HPV Vaccine Introduction* published in 2016 and available at: [http://www.who.int/immunization/diseases/hpv/scaling-up-intro/en/](http://www.who.int/immunization/diseases/hpv/scaling-up-intro/en/)
1. INTRODUCTION
INTRODUCING HPV VACCINE

HPV INFECTION AND CERVICAL CANCER

Cervical cancer is caused by the human papillomavirus (HPV). More than 100 HPV types have been identified to date, about 40 of which can infect the genital area. Two high-risk types of HPV, types 16 and 18, account for about 70% of all cervical cancer cases. HPV can also cause other types of anogenital cancer (vagina, vulva, anus, penis), head and neck cancers, and genital warts in both men and women.

Immunodeficiency is the strongest known cofactor for HPV in cervical and anal cancers. In people living with HIV compared to people who are not, HPV infections are more likely to occur, persist, and progress to cancer.

HPV is sexually transmitted and most people become infected sometime during their lifetime, usually soon after becoming sexually active. Most infections are asymptomatic and usually clear up without any intervention within a few months, and about 90% clear within two years. A small proportion of infections with certain types of HPV can persist and progress to cancer. If infection from cancer-causing HPV types persists over a long period of time, women can go on to develop precancerous lesions that, if left untreated, develop into cervical cancer. This process takes on average 20–30 years from infection to development of cervical cancer.

Although it is preventable, according to the most recent data available (IARC GLOBOCAN 2012), cervical cancer is the fourth most common cancer among women worldwide. It is estimated that each year there are approximately 528,000 new cases and more than 266,000 deaths from cervical cancer. More than 85% of all new cases and deaths occur in less developed countries, partly because routine cervical cancer screening and treatment are not widely available.

Regions with the highest risk include Eastern Africa, Melanesia, Southern and Central Africa (Figure 1). Unless cervical cancer prevention and control measures are successfully implemented, it is estimated that by 2030, approximately 800,000 new cases of cervical cancer will be annually diagnosed. The vast majority of these cases will be in developing countries.

---


INTRODUCING HPV VACCINE

HPV VACCINATION: PART OF A COMPREHENSIVE APPROACH TO PREVENTION OF CERVICAL CANCER

Since 2009, WHO has recommended the inclusion of HPV vaccination into national immunization programmes in countries where cervical cancer is a public health priority and where cost-effective and sustainable implementation of the vaccine is feasible.3

Because HPV vaccines do not protect against all HPV types that cause cervical cancer, vaccine introduction should be part of a coordinated and comprehensive approach to cervical cancer control (Figure 2) that includes:

• Prevention primarily through vaccination of 9-14 year old girls prior to exposure and acquisition of HPV infection;

• Secondary prevention through screening and treatment of adult women for pre-cancerous lesions, and

• Tertiary and palliative care for women affected by cervical cancer.

HPV vaccine introduction should not be deferred in countries where the other relevant interventions are not available. On the contrary, the introduction of HPV vaccine can provide an important strategic opportunity for improving or establishing cervical cancer screening and treatment programmes, and raising awareness of their purpose and availability.

**Figure 2. Programmatic interventions to prevent HPV infections and cervical cancer**

### Population prevalence (not to scale)

<table>
<thead>
<tr>
<th>Age</th>
<th>HPV infection</th>
<th>Precancer</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 years</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**PRIMARY PREVENTION**

- Girls 9-14 years
  - HPV vaccination

- Girls and boys, as appropriate
  - Health information and warnings about tobacco use\
  - Sexuality education tailored to age & culture\
  - Condom promotion/provision for those engaged in sexual activity\
  - Male circumcision

**SECONDARY PREVENTION**

- Women >30 years of age
  - Screening and treatment as needed
  - “Screen and treat” with low cost technology VIA followed by cryotherapy
  - HPV testing for high risk HPV types (e.g. types 16, 18 and others)

**TERTIARY PREVENTION**

- All women as needed
  - Treatment of invasive cancer at any age
    - Ablative surgery
    - Radiotherapy
    - Chemotherapy

---

*A Tobacco use is an additional risk factor for cervical cancer.

---

**A CHECKLIST FOR A COMPREHENSIVE CERVICAL CANCER PREVENTION AND CONTROL PROGRAMME**

1. A functional multi-disciplinary platform to foster partnership and collaboration and set the national agenda ✔
2. A comprehensive national policy or plan on cervical cancer prevention and control ✔
3. National guidelines for health workers for all components of comprehensive cervical cancer prevention and control ✔
4. Financial and technical resources to implement the policy/plan and ensure that services are accessible and affordable to girls and women ✔
5. Communication strategies to educate the community and advocate for support of national policies ✔
6. A training plan in place, as well as supervisory mechanisms for quality control and assurance of the programme ✔
7. HPV vaccination as a population based strategy to an appropriate cohort in the target age group of 9 and 14 year old girls ✔
8. Cervical cancer programme to ‘screen and treat’ every women between 30 and 49 years old at least once in her lifetime ✔
9. A functioning referral system that links screening services with the treatment of precancerous lesions and invasive cancer ✔
10. Functioning monitoring systems to track coverage of HPV vaccination, screening and follow-up treatment ✔
11. Existence of a cancer registry as part of the health information system to monitor cervical cancer incidence and mortality ✔

*Adapted from: Comprehensive cervical cancer prevention and control - WHO guidance, March 2013.*
HPV VACCINES

Currently licensed HPV vaccines prevent cervical cancer by preventing infection by various HPV types. The vaccines are most effective when administered to a person prior to exposure to HPV; the vaccines are not therapeutic and cannot be used for treatment of cervical cancer or HPV infection.

Two HPV vaccines are currently pre-qualified\(^4\) by WHO:

1. A bivalent vaccine (Cervarix\(^6\), produced by GlaxoSmithKline) – protects against two HPV types 16 and 18 that cause the majority of cervical cancers; and

2. A quadrivalent vaccine (GARDASIL\(^5\)/Silgard\(^5\), produced by Merck & Co\(^5\)) – protects against HPV types 16 and 18, as well as HPV 6 and 11 that are responsible for anogenital warts.

As of December 2014, the U.S. Food and Drug Administration (FDA) approved Merck’s 9-valent HPV vaccine (GARDASIL 9\(^5\)) which includes the additional five HPV types 31, 33, 45, 52 and 58 compared to the quadrivalent vaccine. The 9-valent vaccine is currently undergoing WHO review for prequalification.

In females, the 9-valent vaccine is licensed for prevention of cervical, vulvar, vaginal, and anal cancers caused by HPV types 16, 18, 31, 33, 45, 52 and 58, pre-cancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, and genital warts caused by HPV types 6 and 11.

For the 9-valent HPV vaccine, WHO is currently coordinating a review and assessment of the incremental effectiveness (additional preventable disease burden) and cost-effectiveness for

\(^4\) WHO provides a service to UNICEF and other UN agencies that purchase vaccines, to determine the acceptability, in principle, of vaccines from different sources for supply to these agencies. The detailed procedure and most recent list of prequalified vaccines can be found at: http://www.who.int/immunization_standards/vaccine_quality/pq_system/en/

\(^5\) Outside of the U.S.A. Merck is known as MSD Merck Sharp & Dohme.
cervical cancer prevention of immunization with the five additional HPV types, in particular in low- and middle-income countries (LMIC). This review will be complemented with modelling efforts led by independent experts.

**Table 1. Summary of HPV vaccine characteristics**

<table>
<thead>
<tr>
<th>ATTRIBUTES</th>
<th>BIVALENT (CERVARIX&lt;sup&gt;a&lt;/sup&gt;)</th>
<th>QUADRAVLENT (GARDASIL&lt;sup&gt;b&lt;/sup&gt;/SILGARD&lt;sup&gt;b&lt;/sup&gt;)</th>
<th>9-VALENT (GARDASIL 9&lt;sup&gt;b&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine type</td>
<td>Recombinant L1-capsid virus-like particles (VLP)</td>
<td>Recombinant L1-capsid virus-like particles (VLP)</td>
<td>Recombinant L1-capsid virus-like particles (VLP)</td>
</tr>
<tr>
<td>HPV types in vaccine</td>
<td>16,18</td>
<td>6,11,16,18</td>
<td>6,11,16,18, 31,33,45,52,58</td>
</tr>
<tr>
<td>Disease protection</td>
<td>Cervical cancer (and premalignant genital lesions of cervix, vulva and vagina)</td>
<td>Cervical cancer (and premalignant genital lesions of cervix, vulva and vagina)</td>
<td>Cervical cancer (and premalignant genital lesions of cervix, vulva and vagina)</td>
</tr>
<tr>
<td>Genital warts</td>
<td>Genital warts</td>
<td>Genital warts</td>
<td></td>
</tr>
<tr>
<td>Cross-protection against HPV-types</td>
<td>31, 33</td>
<td>31, 45</td>
<td>Not necessary&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Number of doses required</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Dosing interval (flexibility)</td>
<td>0 and 6 months (No maximum interval but suggested not more than 12-15 months)</td>
<td>0 and 6 months (No maximum interval but suggested not more than 12-15 months)</td>
<td>0 and 6 months (No maximum interval but suggested not more than 12-15 months)</td>
</tr>
<tr>
<td>Method of administration</td>
<td>Intramuscular injection</td>
<td>Intramuscular injection</td>
<td>Intramuscular injection</td>
</tr>
<tr>
<td>Presentation and Type of Vaccine Vial Monitor (VVM)</td>
<td>1-dose vial; VVM 30 2-dose vial; VVM 30</td>
<td>1-dose vial; VVM 30</td>
<td>1-dose vial; VVM TBD</td>
</tr>
<tr>
<td>Shelf-life</td>
<td>48 months at 2-8 °C for 1-dose vial; 36 months at 2-8 °C for 2-dose vial; vaccine is freeze sensitive</td>
<td>36 months at 2-8 °C, vaccine is freeze sensitive</td>
<td>36 months at 2-8 °C, vaccine is freeze sensitive</td>
</tr>
<tr>
<td>Contraindications</td>
<td>• Severe allergic reaction to any vaccine component after first dose  • Severe febrile illness  • Known to be pregnant&lt;sup&gt;b&lt;/sup&gt;</td>
<td>• Severe allergic reaction to any vaccine component after first dose  • Severe febrile illness  • Known to be pregnant&lt;sup&gt;b&lt;/sup&gt;</td>
<td>• Severe allergic reaction to any vaccine component after first dose  • Severe febrile illness  • Known to be pregnant&lt;sup&gt;b&lt;/sup&gt;</td>
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</tbody>
</table>

<sup>a</sup> Immunity is based on the actual VLP L1 antigen, so cross protection is unnecessary. Actual VLP antigen produces a much stronger and longer lasting immunogenic response than anything that cross protection might produce.

<sup>b</sup> Inadvertent vaccination is no reason to terminate pregnancy.

Additional information on the different HPV vaccines is available on the WHO website at http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html

Under special conditions, some HPV vaccine products are licenced for Controlled Temperature Chain (CTC) which permits the vaccine to be kept at ambient temperatures not exceeding 40°C for up to 72 hours (See Box 1).
INTRODUCING HPV VACCINE

Box 1. Controlled Temperature Chain (CTC) – beyond the traditional cold chain

The “controlled temperature chain” (CTC) is an innovative approach to vaccine management allowing vaccines to be kept at temperatures outside of the traditional cold chain of +2°C to +8°C for a limited period of time under monitored and controlled conditions, as appropriate to the stability of the antigen. A CTC typically involves a single excursion of the vaccine into ambient temperatures not exceeding +40°C and for duration of a specific number of days, just prior to administration.

WHO has established the following programmatic criteria for a vaccine to be labelled for and used in a CTC:
1. The vaccine should be used in a campaign or special strategy setting. CTC is not currently recommended for immunization through routine delivery.
2. The vaccine must be able to tolerate ambient temperatures of at least +40°C for a minimum of three days and should be accompanied by:
   a. a vaccine vial monitor (VVM) on each vial, and
   b. a peak threshold indicator in each vaccine carrier.
3. The vaccine must be licensed for use in a CTC by the relevant regulatory authorities, with a label that specifies the conditions.

For more information refer to the CTC website at: http://www.who.int/immunization/programmes_systems/supply_chain/ctc/en/

HPV VACCINATION: SOMETHING NEW AND DIFFERENT FOR IMMUNIZATION PROGRAMMES

For many countries, the introduction of HPV vaccine into the national immunization programme is different and considerably more complicated than adding a new infant vaccine. HPV vaccination has a number of special considerations that offer both challenges and opportunities for immunization programmes.

CHALLENGES:

- No existing service delivery platform (or immunization contacts) to access a new target population of 9-14 year old girls. While programmes may have experience reaching this age group with one-time, one-shot vaccination campaigns (e.g. for measles-rubella, yellow fever, meningitis A), the HPV vaccine has a 2-dose schedule.
- Sensitivities around HPV vaccination providing protection against a sexually transmitted infection (STI), offered for girls-only, and recurrent concerns about Adverse Events Following Immunization (AEFIs) and vaccine safety -- despite a solid safety record.
- Requires robust communication and social mobilization to assist with acceptance, ensure completion of schedule, and to decrease costs related to tracking drop-outs. Additionally, preparedness for crisis communication is essential.
- A uniquely high profile vaccine for many countries, with a broad array of stakeholders (other recent new vaccines have not had this variety, complexity, or prominence of partners).
Immunization programmes need to be prepared for HPV vaccination to be championed and/or led by others (who may not be very familiar with immunization).

- **Complex coordination and communication** among many stakeholders (to make decisions, plan, and implement). To be inclusive, new structures and mechanisms often need to be established.

- **Cost** – Not only is HPV vaccine a relatively expensive vaccine to procure, but also the operational costs of vaccine delivery are substantial (depending on the strategy, HPV vaccine delivery costs can be considerably higher than for new infant vaccines).

- **New technical or programmatic issues** such as learning how to properly locate the target population and calculate its accurate size and denominator; adopting new coverage monitoring methods; introducing informed consent processes; dealing with adolescent concerns; etc.

**OPPORTUNITIES:**

- **Demonstrating country commitment and progress on Global Action Plans** -- such as the *Global Vaccine Action Plan (GVAP) 2011-2020* and the *Global Action Plan for the Prevention and Control of Non-Communicable Diseases (NCDs) 2013-2020*.

- **Supporting a comprehensive approach to prevention and control of cervical cancer** because HPV vaccination does not protect against all types of HPV and cervical screening programmes will therefore still be needed, particularly for older women who were not able to benefit from vaccination.

- **Integration** of HPV vaccination with the delivery of other health services for 9-14 year old children, provides opportunities to establish primary care for new age group of children and health system strengthening.

- **Broadening of stakeholders and partners** for immunization, including those from reproductive health, adolescent health, school health, cancer control, HIV prevention, and women’s health.

- **Vigorous new energy and new advocacy** from the various collaborators can create synergies, innovative ways of working, new linkages, broader access, and additional resource mobilization and support for immunization.

Global experience with national HPV vaccine delivery in low and middle income countries is rapidly increasing. Countries are piloting and others adapt their approaches after national introduction. Best practices and learning have been compiled and shared. As with the management of any good programme, the introduction of HPV vaccination will require innovation, openness and flexibility to change, and a commitment to continuous quality improvement processes.

Based on current experience we know that the introduction of HPV vaccination requires substantial and prolonged hard work, strong political will, and adequate financial resources.
KEY RESOURCES

Scaling Up HPV Vaccine Introduction
(http://www.who.int/immunization/diseases/hpv/scaling-up-intro/en/)

This report summarizes key lessons and their implications for action as countries introduce and scale-up HPV vaccination as part of a comprehensive effort to reduce cervical cancer disease and death. Drawing on the Global Learning Meeting on HPV Vaccine Introduction held in November 2015, this report complements other efforts to compile experiences, such as the PATH/ London School of Hygiene and Tropical Medicine (LSHTM) 2015 Lessons Learnt project*.

Specifically, this report offers experiences – many directly reported by country health managers - in the main areas of vaccine introduction: decision-making, planning and coordination, delivery strategies, communication, crises management, monitoring and evaluation, costing and sustainability. This report also offers insights into reaching hard-to-reach populations and on integration of HPV vaccine in both a comprehensive cervical cancer prevention and control plan and into adolescent health programming.

* http://www.rho.org/HPVlessons/index.htm

HPV Vaccine Introduction Clearinghouse
(http://www.who.int/immunization/hpv/en/)

The HPV Vaccine Introduction Clearing House is a unique space to find WHO publications, tools and other important resources on the human papillomavirus vaccine (HPV).

Its purpose is to help guide HPV vaccine policy, programme and communications managers in the development of successful strategies for the introduction and sustained delivery of HPV vaccination at a national level.

The clearinghouse’s 5 areas are:

- **LEARN**
  - Learn about cervical cancer, HPV and HPV vaccines.

- **PLAN**
  - Decide and plan for HPV vaccination introduction.

- **TARGET**
  - Understand and target young people and those who influence them.

- **DELIVER**
  - Deliver HPV vaccination taking into account its unique challenges.

- **COMMUNICATE**
  - Communicate about HPV vaccination using research-based approaches.
WHO RECOMMENDATIONS FOR HPV VACCINATION

Human papillomavirus vaccines: WHO position paper – October 2014

WHO will be revising its HPV Vaccine Position Paper in 2017, in light of the SAGE October 2016 recommendations. The main changes will include a focus on 9-14 year olds and recommendation for vaccinating multiple age cohorts when HPV vaccine is first introduced to result in faster population impact.

**WHO recommends** HPV vaccines should be included in national immunization programmes, provided that: prevention of cervical cancer and/or other HPV-related diseases constitute a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost effectiveness of vaccination strategies in the country or region is considered.

HPV vaccines should be introduced as part of a coordinated and comprehensive strategy to prevent cervical cancer and other diseases caused by HPV. This strategy should include education about reducing behaviours that increase the risk of acquiring HPV infection, training of health workers and information to women about screening, diagnosis and treatment of precancerous lesions and cancer. The strategy should also include increased access to quality screening and treatment services and to treatment of invasive cancers and palliative care.

The introduction of HPV vaccine should not undermine or divert funding from developing or maintaining effective screening programmes for cervical cancer. HPV vaccination is a primary prevention tool and does not eliminate the need for screening later in life, since the vaccines do not protect against all high risk HPV types.

Opportunities to link the introduction of HPV vaccine to other programmes targeting young people should be sought (e.g. through adolescent health services).

However, the introduction of HPV vaccination should not be deferred because other relevant interventions cannot be implemented at the same time.

Experience with various delivery strategies including campaigns, health facility, and outreach/school-based is still accumulating. Countries should use approaches that are (i) compatible with their delivery infrastructure and cold chain capacity (ii) affordable, cost-effective and sustainable and (iii) achieve the highest possible coverage. If countries consider phased introduction, priority should be given to strategies that include populations which are likely to have less access to screening for cervical cancer later in life.

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Recommended target age and vaccination schedule

- Girls aged 9-14 years* prior to becoming sexually active.
- 2 doses with a 6 month interval.
- There is no maximum interval between the 2 doses, however, an interval of not greater than 12-15 months is suggested to enable girls to complete the schedule promptly before becoming sexually active.
- If the interval between doses is shorter than 5 months, then a 3rd dose should be given at least 6 months after the first dose.
- A 3-dose schedule (i.e. at 0, 1-2, and 6 months) is recommended for females 15 years and older, and for those known to be immunocompromised and/or HIV-infected (regardless of whether they are receiving antiretroviral therapy). It is not necessary to screen for HPV infection or HIV infection prior to HPV vaccination.

HPV vaccination of males: is not recommended as a priority, especially in resource-constrained settings, as the available evidence indicates that the first priority should be for cervical cancer reduction by timely vaccination of young females and high coverage with each dose.

Vaccine safety: Both HPV vaccines have excellent safety and efficacy profiles. Adverse events following HPV vaccination are generally non-serious and of short duration.

Contraindications: Severe allergic reaction to a previous vaccine dose or vaccine component; Pregnancy; Acute severe febrile illness. However, the presence of a minor infection, such as a cold, is not a contraindication for immunization.

Co-administration: HPV vaccine can be co-administered with other non-live and live vaccines using separate syringes and different injection sites.

Vaccine interchangeability: The two WHO prequalified HPV vaccines have different characteristics, components and indications, and in settings where both may be in use, every effort should be made to administer the same vaccine for all doses. However, if the vaccine used for prior dose(s) is unknown or unavailable, either of the two HPV vaccines can be used to complete the recommended schedule.

Monitoring: As with the introduction of any new vaccine, post-marketing surveillance to monitor safety should be in place. Complete and accurate monitoring of HPV vaccine coverage by dose and by age is needed for programme performance monitoring. Monitoring HPV disease is not a prerequisite to initiating HPV vaccination. However, all countries should consider establishing, or improving, reporting to comprehensive cancer registries or specific cervical cancer registries.

* Vaccination of older adolescent females or young women is recommended only if this is feasible, affordable, cost effective, and does not divert resources from vaccinating the primary target population (girls 9-14 years) or from effective cervical cancer screening programmes.
2. DECISION-MAKING AT COUNTRY LEVEL
WHAT SHOULD BE THE PROCESS?

It is important to have a systematic and transparent process for making a decision about introducing HPV vaccine into the national immunization programme. Ideally, the national immunization technical advisory group (NITAG) or an equivalent independent advisory body should be requested to undertake a rigorous review of the evidence and make an independent recommendation to the national government.

NITAG members should have a broad health perspective to ensure that the impact of HPV vaccine (or any other new vaccine) on the immunization programme and the overall health system is considered.

The NITAG committee and its members must be perceived as objective, independent and not representing a particular interest group. The independence of the NITAG and its reliance on evidence-based decision-making reinforces the credibility of the decision, helps to resist pressure from interest groups and enhances the ability to secure government and/or donor funding for the vaccine introduction. NITAGs function best when they are supported by a secretariat or technical sub-committee to collect and synthesize the evidence.

Subsequently, the Inter-agency Coordinating Committee (ICC) can serve to coordinate partner activities and contribute funding for the immunization programme. As with other decisions pertaining to the national immunization schedule, the national government is responsible for taking the decision to introduce (or not to introduce) HPV vaccine.

KEY RESOURCE

*Principles and Considerations for adding a vaccine to a national immunization programme: From decision to implementation and monitoring*

A generic guide for countries explaining the principles and issues to be considered when introducing a new vaccine into a national immunization programme.

It describes the process and includes the latest references and tools/checklists for:
- vaccine decision-making
- economic analyses
- developing an introduction plan
- cold chain
- integrated disease control and health promotion
- vaccine safety
- communications
- monitoring

Importantly, this guide highlights ways to use the opportunity of adding a new vaccine to strengthen immunization and health systems.


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1 NITAGs should consist of national experts in a broad range of disciplines – such as senior paediatricians, immunization and vaccine experts, epidemiologists, public health experts, health economists, health systems experts and social scientists – who are capable of analysing the different types of scientific evidence and issues that should be considered in making an informed decision.

2 More information and references on NITAGs can be found at: http://www.who.int/immunization/sage/national_advisory_committees/en/

3 A committee made up of representatives of the Ministry of Health (MOH), WHO, UNICEF, and other domestic and external partners to improve coordination among partners for the support of the national immunization programme.
Many times a high-level advocate or "champion", such as the First Lady, can be a key driver to initiate country discussion and decision-making about HPV vaccination. Immunization managers need to be prepared and aware that the first expression of interest about HPV vaccination may come from outside the immunization programme, which enhances the need for the NITAG to be involved.

WHAT INFORMATION IS NEEDED?

The decision to introduce HPV vaccine needs to consider the following:

• Data on the burden of cervical cancer;
• Existence of a National Cancer (or Cervical Cancer) Strategic Plan;
• Current availability and use of other cervical cancer prevention methods (e.g. screening and treatment);
• Immunization coverage and experiences from any vaccines already given to young adolescents;
• Proposed delivery strategy (or strategies), and an analysis of the proportion of girls who would be reached using the proposed strategy;
• Cost, cost-effectiveness, and affordability;
• Overall capacity and performance of the national immunization programme;
• Experience with HPV vaccine introduction from other countries with similar level of development and health system capacity.

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4 If local data are incomplete or not available, the International Agency for Research on Cancer (IARC) and WHO GLOBOCAN 2012 project (http://globocan.iarc.fr/) provides estimates of the incidence of, mortality and prevalence from major types of cancer, at national level, for 184 countries of the world. For a quick access to a summary of the burden of cancer in a country or for a cancer, use the FACT SHEETS option. Fact Sheets are a collection of statistical summaries for the eight most common cancer types or for each country or region of the world. They were developed to provide a quick overview of frequently-requested cancer incidence, mortality and prevalence statistics.

RESOURCES EXCERPT

Scaling-up HPV Vaccine Introduction (WHO, 2016)

Decision-making: Implications for Action

- Gaining the support of high-level advocates, such as First Ladies, can have a major impact on the decision to introduce HPV vaccine.
- Prepare evidence: Investigating and reporting on the cervical cancer burden; cost-effectiveness, feasibility and acceptability provides important information for decision-makers.
- Coordination with the right stakeholders from the beginning will ensure all the players are at the table when it’s time to make decisions and implement. The Health, Education and Finance Ministries are particularly important.
- Prepare for a process involving the policy committees, regulatory bodies, political and financial processes to ensure the decision is anchored in country policies and budget.
- Consider sustainable funding. Donations and external support can help a country introduce HPV vaccine in the short-term, but countries will need to contribute a portion of funding, and advocates should have a plan to secure funding for longer-term sustainability.

WILL HPV VACCINATION BE FINANCIALLY SUSTAINABLE?

Financial sustainability is a key cornerstone for any new vaccine introduction. Sustainability for programme administration is more than the ability to purchase HPV vaccine, but also includes financing of any additional expenses incurred by adapting the immunization programme for the introduction or for new delivery strategies. A costing study is a particularly important assessment to conduct for HPV vaccine introduction as the target population has not previously been a part of the routine immunization programme and the delivery of the vaccine may be primarily outside of health centres (at schools or other outreach locations).

WHO has developed a Cervical Cancer Prevention and Control Costing (C4P) Tool to assist countries to assess both the financial and economic five-year costs of HPV vaccine introduction (see Key Resource below).
WHO Cervical Cancer Prevention and Control Costing (C4P) Tool

Available in both English and French, WHO has developed a generic costing and planning tool for cervical cancer prevention and control. The tool helps programme planners and managers to generate annual cost projections over a five-year period to scale up activities within the health system. The generic version of the WHO C4P tool allows the user to define different vaccine delivery strategies i.e. through schools, health facilities or campaigns, such as national immunization days. Furthermore it allows sub-national segmentation, extensive modification of inputs, a strategic approach, resource allocation, and recognition of prevailing prices and other key variables. It also provides access to transparent underlying calculations and assumptions. The tool is pre-populated with the required data, and linked to data sources.

The WHO C4P tool consists of a HPV Vaccine Module and a Cervical Cancer Screening and Treatment Module.


WHAT INFORMATION IS AVAILABLE ABOUT THE PRICE OF HPV VACCINES?

Vaccine product, price, and procurement data are essential to forecasting, budgeting, and identifying sustainable financing for new and priority vaccines. In particular, because vaccine price is an important component of health budgets, the price of a vaccine is a major factor in deciding when to adopt and whether to sustain new vaccines.

However, many countries lack access to information on vaccine prices and can be uncertain about whether they are able to negotiate equitable and fair prices from manufacturers. There have been many calls (particularly from Middle Income Countries) at the World Health Assembly for greater price transparency.

Some vaccine prices are published by individual countries and by large pooled procurement groups such as the UNICEF Supply Division\(^6\) and the PAHO Revolving Fund\(^7\). WHO has also created a specialize Vaccine Product, Price and Procurement (V3P) Web Platform that brings together price information for all available sources and participating countries (See Key Resource). Information on HPV vaccine prices is included in V3P.

\(^6\) http://www.unicef.org/supply/index_57476.html
\(^7\) www.paho.org/revolvingfund
INTRODUCING HPV VACCINE

KEY RESOURCE

Vaccine Product, Price and Procurement (V3P) Web Platform
http://www.who.int/immunization/v3p

The V3P web platform provides information on vaccine product, price and procurement data with the goal of increasing price transparency and informing decisions around vaccine introduction and implementation.

1. Price Database
The price database contains information on and analyses of vaccine prices and procurement modalities as reported by participating countries and partners, including PAHO revolving fund and UNICEF.

2. Information Repository
The information repository contains documents produced by V3P, including user guidelines and tools, project updates, and analyses.

3. Resource Gateway
The resource gateway is a web portal that offers links to websites providing pertinent information on vaccine product characteristics, price, and procurement.

WHAT DELIVERY STRATEGY FOR HPV VACCINATION IS BEST?

Deciding the delivery strategy for HPV vaccination is an important issue that needs to be considered carefully by each country. The pros/cons, costs, and likely success of different strategies vary according to the country-specific context.

In general, the ideal strategies for delivery of HPV vaccine should be:
• compatible with existing vaccine-delivery infrastructure and cold chain capacity;
• affordable, cost-effective and sustainable;
• able to achieve the highest possible coverage.

In practice, countries may need to balance strategies that maximize coverage with those considered most feasible, affordable and sustainable.
Box 2. A word about cost:

Many countries have found that the cost of implementing an HPV vaccination programme is significant. Costs vary by country, by strategy (health facility, school-based or other outreach, campaign), by frequency of vaccination (continuous, monthly, periodic), and by geographical setting (urban, rural, mountainous areas, etc.).

Currently available, preliminary data based on WHO-PATH analysis* suggest that for GAVI-eligible countries:

• Start-up costs per girl for vaccine delivery are ~ USD$3-5.
• Operational costs for delivering 2 doses per eligible girl are ~ USD$3-4.
• During introduction year, total start-up and operational costs for delivering 2 doses per eligible girl is ~ USD$5-7 (excluding vaccine cost).


In deciding on the delivery strategy for HPV vaccination it is important to prioritize two considerations:

1. Reaching girls who, later in life, will be least likely to have access to cervical cancer screening; and,
2. Wherever possible, selecting approaches that would provide opportunities for integration with other adolescent health services.

It is likely that no single delivery strategy is able to meet all the programme objectives. Ultimately, a combination of strategies may be needed to achieve high coverage and avoid disruption of established services while optimizing resources.

For HPV vaccination there are several commonly used strategies:

• Vaccine delivery at health-care facilities
• Vaccine delivery through outreach:
  • School-based outreach
  • Other outreach
• Vaccine delivery through campaigns

Each strategy has pros and cons. It may be necessary to use a combination of strategies to ensure access for all eligible girls. This is especially true if the young girls targeted for HPV vaccination live both in urban and rural communities, including locations distant from health-care facilities, and if a proportion of them are transient and/or homeless.

HPV VACCINE DELIVERY AT HEALTH-CARE FACILITIES

Similar to the infant vaccination programme, this approach provides HPV vaccination to eligible girls at 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 facility.

Both high and low income countries have shown that it is possible to achieve national HPV vaccine coverage over 70% through offering vaccination at health centres. This strategy has also been
shown to achieve more coverage if offered as “vaccination days” with minor incentives for girls who attend, such as short waiting periods, music, discussion groups and/or videos in the waiting room.

However, a fixed-site, health-care facility delivery strategy may not be effective if girls find it difficult to attend the clinic (for example, if the opening hours are not convenient, or if they are shy or uncomfortable for any reason), or if the majority of girls do not have easy access to a health facility.

School or school health programmes can have an active role in a facility-based delivery strategy. For example, in some countries schools are notified on a specific day to bring girls to the health facility (or nearest scheduled outreach session) for vaccination.

**HPV VACCINE DELIVERY THROUGH OUTREACH**

In the context of immunization, outreach refers to any strategy that requires health workers to leave their facility in order to transport and deliver immunization services to a variety of fixed or mobile sites close to large numbers of target-aged girls. Some examples of outreach venues are community centres, school buildings and, if appropriate and with the support of those in charge, places of worship, and other places where people tend to gather.

**School-based (outreach) strategy**

For girls living in distant communities and others who cannot attend clinic services, a potential strategy is school-based vaccination. To select eligible girls for vaccination, a school-based strategy may choose to target all girls in one or more selected school year/grade/class, although it is also acceptable to use age-based eligibility.

A school-based strategy can serve as an opportunity to create or strengthen school health services and improve health education and communication.

Where school health programmes exist and a designated healthcare worker (based either at the school or health facility), provides regular health services at the school, this person can be trained and charged with vaccinating target-aged girls with HPV vaccine as part of their school-based health duties (if the national policy permits). The operational costs of adding HPV vaccine delivery to an existing and already funded school health programme infrastructure may be minimal (assuming that the costs for salary, per diems, and transport are already provided in the health budget).

If, however, a school health programme with designated healthcare staff does not exist, a school-based delivery strategy will require the health facility staff to travel away from the health centre for several days to reach all the schools in their catchment area. This can be expensive (additional resources needed) and disruptive to regular services to implement. It may also be inefficient if school enrolment of target aged girls is low.

To ensure equitable access to HPV vaccine, where a large proportion of eligible girls are not enrolled in school or there are high rates of absenteeism, a school-based strategy must be supplemented by other efforts to reach girls who are not in school. Teachers and community workers and leaders can play important roles in identifying these girls, educating, motivating and assisting them to access vaccine services at other sites.
Before implementing school vaccination programmes, countries need to be able to assess the capacity, strengths, and weaknesses of their school and health systems to support such programmes.

Undertaking a readiness assessment will aid countries in their decision-making and planning, but can also be used by countries wishing to improve the performance of their existing school vaccination activities.

The 3 primary purposes of the School Vaccination Readiness Assessment Tool are:

1. To help Ministries of Health and Education determine, monitor, and improve their country’s overall readiness to conduct school vaccination activities.

2. To provide a simple-to-use assessment of a country’s overall capacity and specific strengths and weaknesses to implement school vaccination activities.

3. To guide a process to improve overall readiness and initiation of a new school vaccination programme or to improve an existing one.

While this Readiness Assessment Tool is specifically designed to assess country-wide readiness to implement school vaccination, it might also provide information useful for assessing and subsequently improving broader school health services.


Education statistics such as those collected by UNESCO⁸, can be useful to gain an understanding of the age profile of those who attend schools and those who do not. Another resource is the “All in school, Out of school” reports and online tool⁹.

Other outreach strategies

When a large proportion of the population lives in areas with limited access to health facilities and there is low school attendance for target-aged girls, an outreach delivery strategy at a convenient location (e.g. marketplace, community gathering place) may be appropriate and help to ensure equitable vaccination opportunities for “hard-to-reach” girls.

Outreach sessions should be planned to ensure all girls are reached with the required HPV doses. The interval between 2 HPV doses must be at least 5 months. Therefore, HPV vaccination outreach sessions could be planned every 6 months, or even annually, to reach all target girls with 2 doses. Depending on the schedule for outreach for infant vaccination, it may be possible to combine it with the HPV vaccination outreach (i.e. offer HPV vaccination at the infant vaccination outreach). This requires good communication and social mobilization so that the girls are informed that vaccination for their age-group is being offered.

As mentioned earlier, some countries are trying an approach where they notify schools on a specific day to bring girls to the nearest scheduled outreach (or fixed facility) for HPV vaccination.

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⁹ http://allinschool.org/resources/reports/
IN INTRODUCING HPV VACCINE

VACCINE DELIVERY THROUGH CAMPAIGNS

In some instances, there may be benefits or opportunities to deliver HPV vaccine via a large-scale vaccination campaign strategy.

For example, if a country can afford it and they wish to “catch up” the entire cohort of 9-14 year old girls when the HPV vaccine is first introduced, then planning two rounds of national HPV immunization days with an interval of 6 months, or one campaign annually, may be an option.

Some countries have made use of existing campaign days, e.g. Child Health Days/Weeks, Measles/Rubella or tetanus toxoid (TT) supplementary immunization activities (SIAs), and successfully added HPV vaccination. However, most often the frequency of campaign opportunities that could include HPV vaccination is insufficient to ensure delivery on a routine basis, year after year, of HPV vaccine. Nonetheless, campaigns can be helpful to “kick start” activities.

In countries with very small and difficult to access populations, (for example, island states) the use of a campaign strategy for HPV vaccination may be the most practical and cost-effective. Such countries could conduct a campaign (either with two rounds in a year, or annually for two consecutive years) targeting all the girls 9-14 years. This strategy could be repeated every 5 years to ensure complete coverage of the next cohort of girls 9-14 years.

It is important to note, that any campaign strategy for the delivery of HPV vaccine needs to ensure the recording of the doses administered on the girls vaccination cards. (See Key Resource page 65: Practical Guide for the design, use and promotion of home-based records in immunization programmes)

Table 2 provides summary of considerations for different HPV vaccination delivery strategies. In practice, a balance of the pros and cons will need to be made. 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. For more information on country experiences using different HPV delivery strategies and reaching hard-to-reach girls see companion document Scaling-up HPV Introduction (WHO, 2016).

Table 2. Considerations for different HPV vaccine delivery strategies

<table>
<thead>
<tr>
<th>CONSIDERATIONS</th>
<th>DELIVERY STRATEGY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HEALTH FACILITY</td>
</tr>
<tr>
<td>Access</td>
<td>Girls must come to health centre</td>
</tr>
<tr>
<td></td>
<td>Parents may be present at time of vaccination</td>
</tr>
<tr>
<td></td>
<td>Does not require health workers to leave post</td>
</tr>
<tr>
<td>Equity</td>
<td>In- and out-of school girls</td>
</tr>
</tbody>
</table>
### CONSIDERATIONS

<table>
<thead>
<tr>
<th>DELIVERY STRATEGY</th>
<th>HEALTH FACILITY</th>
<th>OUTREACH</th>
<th>COMMUNITY OUTREACH</th>
<th>CAMPAIGN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Community mobilization</strong></td>
<td>May need more intensive mobilization for girls to attend</td>
<td>Schools can help to facilitate sensitization and mobilization of parents/communities</td>
<td>Same outreach locations as for infant vaccinations may make mobilization easier</td>
<td>Needs strong mobilization effort</td>
</tr>
<tr>
<td><strong>Frequency of vaccinations</strong></td>
<td>Continuous vaccine availability possible all year</td>
<td>Requires at least 1-2 visits to schools per year</td>
<td>Vaccine available only when outreach session planned</td>
<td>Requires at least 1-2 rounds per year</td>
</tr>
<tr>
<td><strong>Vaccine supply</strong></td>
<td>Continuous vaccine supply available with other routine vaccines</td>
<td>Enrolment lists can facilitate estimates of vaccine supply</td>
<td>Challenging to know exact number of girls who will attend outreach session</td>
<td>Large volume of vaccine needed over short duration Distribution challenges (must be able to redistribute/re-supply quickly during campaign)</td>
</tr>
<tr>
<td><strong>Cold chain management</strong></td>
<td>Cold chain available at health centre</td>
<td>Vaccine carriers must be prepared to maintain cold chain</td>
<td>Vaccine carriers must be prepared to maintain cold chain</td>
<td>Vaccine carriers must be prepared to maintain cold chain May be able to use Controlled Temperature Chain (CTC)</td>
</tr>
<tr>
<td><strong>Integration with other interventions</strong></td>
<td>Help to strengthen Adolescent Friendly Health Services</td>
<td>Co-delivery with short-duration interventions possible School health platform</td>
<td>Co-delivery with short-duration interventions possible</td>
<td>Integrate with other campaigns (e.g. Child Health Days/Weeks)</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>Low as supported by national health budget</td>
<td>Medium-High (depends if school health programme is already funded or if additional resources are required for facility healthcare workers to travel to schools)</td>
<td>Medium-High (depends if using existing outreach sessions that are already planned and funded)</td>
<td>Generally high (but for small populations may be more cost-effective) Additional budget for per-diems and transport, etc.</td>
</tr>
</tbody>
</table>

*Note: A combination of strategies may be needed to achieve high coverage while optimizing resources and to include out-of-school/hard-to-reach/vulnerable target aged girls. Strategies may also vary throughout a country, based on local/provincial/district characteristics or opportunities.*
INTRODUCING HPV VACCINE

HOW CAN HPV VACCINE BE INTEGRATED WITH OTHER VACCINATIONS OR HEALTH INTERVENTIONS?

HPV vaccine introduction may provide impetus to health officials and policy makers to improve and strengthen other health services at national, regional, and local levels. For example, addressing structural or systems barriers that may prevent young adolescent girls from receiving HPV vaccine may facilitate adolescent access to other health interventions. Community health worker networks can be mobilized to assist adolescents in accessing various health services, and vaccine introduction may also serve as an opportunity to improve adolescent health education. Health communication is a key component to successful HPV vaccine implementation, and can be used to deliver a variety of other health messages as well.

Table 3. Short duration interventions that may be combined with HPV vaccine delivery

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>INTERVENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Vision screening (if referral/glasses available and affordable)</td>
</tr>
<tr>
<td>Commodities and treatment</td>
<td>Anti-helmintic treatment (de-worming)</td>
</tr>
<tr>
<td></td>
<td>Insecticide treated bednets for malaria control</td>
</tr>
<tr>
<td></td>
<td>Iron and folic acid supplementation</td>
</tr>
<tr>
<td>Information and life skills</td>
<td>Promotion of physical activity and exercise</td>
</tr>
<tr>
<td></td>
<td>Prevention of mosquito-borne diseases</td>
</tr>
<tr>
<td></td>
<td>Menstrual hygiene education, with products, if relevant for age group targeted for HPV vaccination</td>
</tr>
<tr>
<td>Other vaccines</td>
<td>All vaccines can be co-administered with HPV vaccine. Particular opportunities for the target group may be found with Td/Tdap boosters, catch-up of HepB and measles/rubella vaccination, and dengue vaccination (if applicable)</td>
</tr>
</tbody>
</table>


Delivering HPV vaccination with other interventions may promote sharing of resources and knowledge across programmes, optimize costs and logistics, and serve to integrate a variety of services in a more efficient, effective and sustainable way. It will be important to select an intervention that is age-appropriate, effective, and that will not negatively impact HPV vaccine delivery.
 INTRODUCING HPV VACCINE

KEY RESOURCE

Options for linking health interventions for adolescents with HPV vaccination

There are few interventions targeting young adolescents and those that do exist are often not adequately reaching them. This is because the number of contacts of adolescents with the health system is generally low.

Immunization programmes are well known for achieving good coverage and this short brochure outlines the opportunities that the introduction of HPV vaccination can provide an entry point for other health interventions targeting 9-14 year olds. A number of health interventions are suitable for joint delivery with HPV vaccination and can foster synergies between the Expanded Programme on Immunization (EPI) and school and/or adolescent health programmes.

www.who.int/immunization/diseases/hpv/linking_h_interventions/en/

See additional Key Resources on adolescent health below

KEY RESOURCES – ADOLESCENT HEALTH

Health for the World’s Adolescents is a dynamic, multi-media, online report. It describes why adolescents need specific attention, distinct from children and adults. It presents a global overview of adolescents’ health and health-related behaviours, including the latest data and trends, and discusses the determinants that influence their health and behaviours. It also features adolescents’ own perspectives on their health needs.

In addition to the online report, a summary was produced in print format in Arabic, Chinese, English, French, Russian and Spanish.

http://www.who.int/maternal_child_adolescent/topics/adolescence/second-decade/en/
KEY RESOURCES – ADOLESCENT HEALTH (continued…)

The largest generation of adolescents in human history (1.8 billion) face unprecedented social, economic, and cultural change according to a new *Lancet* Report (May 2016): *Our Future: A Lancet Commission on Adolescent Health and Wellbeing*.

The Report and related Commission bring together perspectives from public health, economics, political and social science, behavioural science and neuroscience to consider strategies to advance adolescent health and wellbeing, and call for adolescents themselves to be part of the change and accountability mechanisms.


To support the implementation of the new Sustainable Development Goals (SDGs) that came into effect January 2016, the UN Secretary-General has called for new and refreshed commitments to the Every Woman Every Child *Global Strategy for Women’s, Children’s and Adolescents’ Health*. For the first time, the health of adolescents has been highlighted for global attention.

http://globalstrategy.everywomaneverychild.org/pdf/EWEC_globalstrategyreport_200915_FINAL_WEB.pdf

http://globalstrategy.everywomaneverychild.org/

As an operational companion guide, the *Global Accelerated Action for the Health of Adolescents* (AA-HA!) will be submitted to the 2017 World Health Assembly. This resource will provide countries with evidence-based interventions and implementation guidance for improving adolescent health.

WHAT POLICIES NEED TO BE IN PLACE?

As a part of the decision-making process for HPV vaccines, the existence and implementation status of the following policy issues should be reviewed:

- Existence of a school health and/or adolescent health programme, services and interventions available, effectiveness and reach of the programme, and links to the national immunization programme.
- Policies and legislation concerning vaccination at school.
- Informed consent process for routine immunization services and vaccines delivered during campaigns, and the applicability of these policies for HPV vaccines delivered to girls aged 9-14 years.
- Policies and strategic plans related to the prevention of cervical cancer, and the potential role of HPV vaccination in these policies and plans.

KEY RESOURCE

Considerations regarding consent in vaccinating children and adolescents between 6 and 17 years old

Around the world, immunization programmes are increasingly including, in their national immunization schedules, vaccines that target age groups beyond infancy and early childhood.

This document is aimed at programme managers who are planning to introduce vaccines for older children and adolescents aged between 6 and 17 years.

It provides information that should be considered when preparing guidance notes on the consent process, or for clarifying questions from the health workers who provide the vaccinations.

The document is all the more important because the target population group for HPV vaccine may present for vaccination without an accompanying parent or legal guardian.

www.who.int/immunization/programmes_systems/policies_strategies/consent_note/en/
WHO ARE KEY STAKEHOLDERS TO INCLUDE IN THE PROCESS?

Successful introduction of HPV vaccine as part of a comprehensive cervical cancer control strategy will require collaboration of the immunization programme with a variety of stakeholders within and across programmes and sectors at different levels of government.

Close collaborations with cancer, adolescent health, women’s health, and/or sexual and reproductive health programmes can foster supportive partnerships for HPV vaccine introduction. School-based strategies are an opportunity to collaborate with school health programmes where they exist, and more broadly, with the Ministry of Education to integrate public health messages within schools. Ongoing communication among stakeholders before, during, and after vaccine introduction is essential for successful implementation.

Advocacy with and engagement of medical and nursing associations, national leaders, parliamentarians, and other stakeholders will be essential to ensure high HPV vaccination coverage and awareness of the need to strengthen cervical cancer screening.

Ultimately, a country should have developed a National Cancer Strategy within which activities to prevent cervical cancer are situated. It is similarly important for countries to establish population-based cancer registries in order to measure the burden of cancer in communities and assess the impact of interventions.

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3. PLANNING
WHAT PLANS NEED TO BE MADE OR REVISED?

Once a decision has been taken to introduce HPV vaccine, a detailed planning process will need to be conducted. The target population, delivery strategy, vaccination schedule, and logistics need to be carefully considered and the national comprehensive multi-year plan for immunization (cMYP) updated. Step-by-step guidance is provided in the WHO/UNICEF Guidelines for developing a comprehensive multi-year plan (cMYP) document available from the WHO website.1

In addition to updating the cMYP to include HPV vaccine, a detailed introduction plan will need to be developed. The plan should outline all activities and steps required for a successful introduction by programme component, identify government departments, institutions or external partners that are responsible for each activity, and include a timeline and detailed budget.

Given the unique considerations for HPV vaccine introduction, it is critical that countries allow enough time for planning and implementation of all the specified introduction activities and that the introduction is not rushed. Sequencing activities in a detailed chronogram will highlight critical milestones necessary for the HPV vaccine introduction to proceed smoothly.

Countries are encouraged to refer to the checklist and tools contained in the WHO guide Principles and considerations for adding a new vaccine to a national immunization programme: From decision to implementation and monitoring (See Key Resource page 13). In particular:

Annex 3: Template for a new vaccine introduction plan.


Both of these annexes can be downloaded in an Excel format.2

HOW TO PLAN FOR NATIONAL INTRODUCTION?

Immunization programmes without prior experience of routinely delivering multi-dose vaccinations to 9-14 year old girls may benefit by planning a phased introduction of HPV vaccine. This enables the identification and resolution of challenges and barriers before national scale-up.

Delivering HPV vaccine on a small scale (e.g. 1-2 districts or states/provinces with different characteristics such as, urban/rural, high/low coverage, different levels of school attendance, etc.) allows the national immunization programme to:

• fine tune training and communication plans
• evaluate vaccine acceptability by the community and health professionals
• determine the communication and social mobilization strategies necessary to establish and sustain high coverage for HPV vaccine
• learn how to best access the target age group
• identify the human and financial resources required
• consider whether the proposed delivery strategies are sustainable

HOW TO SELECT THE TARGET POPULATION FOR HPV VACCINATION?

National strategies for HPV vaccination should prioritize high coverage in the primary target population of 9-14 year old girls, prior to the onset of sexual activity, as HPV vaccination is most effective when administered prior to exposure to HPV types in the vaccine.

WHO now recommends the vaccination of multiple cohorts of girls 9-14 years when HPV vaccine is first introduced. This has cost implications but results in faster population impact than vaccination of single age cohorts. After the initial vaccination of all girls 9-14 years (or some subset), in the subsequent years going forward, only one age cohort will need to be targeted (e.g. 9 year old girls).

However, if countries have resource limitations that prevent initial multiple cohort vaccination, a single year cohort (or school grade) of girls within the age range of 9-14 years can be selected as the target population for HPV vaccination.

Deciding which age or grade cohort to target for HPV vaccination is an important decision that should consider local factors such as:

- Average age of becoming sexually active. For example, if it is common for girls to marry at 12-14 years of age, then it would be best to provide HPV vaccine at a younger age.
- If knowledge of age is culturally or socially unimportant/limited, it may be better to target an age that is a rounded number for example, 10 years, rather than 9 or 11 years. Anecdotally, it is reported that recall of whole years is more accurate.
- If girls tend to drop-out of school as they get older, it may be better to target the earlier school grades.
- Etc… Consider whatever information is relevant for the particular country context.

Ideally, the choice of what age cohort or grade to target for HPV vaccination should be driven by a good understanding of where the highest number of girls can be found and easily reached, in order to achieve high coverage.

HOW TO DETERMINE THE AGE OF GIRLS WHO ARE ELIGIBLE FOR HPV VACCINATION?

Once a specific target age group has been chosen, the next step is to decide how this age will be determined in order to identify the girls who are eligible for HPV vaccination. There are two common practices:

- By age at time of vaccination, e.g. all 10 year old girls;
- By year of birth, e.g. all girls born in the year 2005.

Deciding which approach to use will depend upon the delivery strategy and the frequency of vaccination contacts (e.g. continuous if facility-based, or 1-2 times per year if outreach) and the level of knowledge/documentation of birth dates.

**By age at time of vaccination, e.g. all 10 year old girls**

With this approach, eligibility for HPV vaccination is based on the age at the time of the first dose, using the date of birth of the girl – at least the month and the year.

Regardless of the location of vaccination (at the health facility or at an outreach site, such as a school) this approach requires the girls to know their age, or for the vaccinator to have access to some documentation (e.g. register, enrolment list) for which the age of the girl can be confirmed.
Determining eligibility using “age at time of vaccination” is an approach which is best suited to strategies that offer HPV vaccination continuously – for example, facility-based vaccination. Girls are told to come for vaccination when they have reached a certain age, if they come before then they are told to return after they have had their birthday. There is a risk that they will forget or not be able to return, but if they do, the HPV vaccine will be administered to them.

Determining eligibility by “age at time of vaccination” can be problematic for outreach strategies that take place only once or twice a year. For example, for a twice yearly school-based outreach, not all girls will have had their birthday when the outreach vaccination team visits. Some may only be of eligible age at the time of the 2nd outreach visit (so they can get their first dose then) but they will have to wait until the next time to complete their schedule.

**By year of birth e.g. all girls born in the year 2005**

Eligibility for vaccination based on the “year of birth” may be programmatically easier to implement for all delivery strategies. This approach determines, for example, that all girls born in 2005 are eligible because they all will have turned 10 years of age by the end of calendar year 2015. In this scenario, when the HPV vaccine is introduced it is announced that all girls born in 2005 should receive HPV vaccination. Regardless of when the vaccine doses are offered or administered, the cohort who is eligible in that year receives the vaccination. Additionally, in places with limited knowledge or records for exact date of birth, girls, parents, health workers, and teachers may be more likely to know or determine a year of birth using significant events or cultural milestones as reminders.

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**Box 3. A word on using a single school grade/class as a “proxy” for the target for HPV vaccination (e.g. all girls enrolled in primary school Grade/Class 5)**

For countries that are planning to deliver HPV vaccination primarily using a school-based outreach strategy it may be tempting to simply select the girls in a particular grade as the target population (e.g. all the girls in Grade/Class 5). However, caution is advised. A grade/class is a proxy for girl’s year of age, not the other way around. If a grade-based target group is to be used, it must be chosen following an assessment of the age span in the grade.

For example, if a country decides to vaccinate 10 year old girls then it is necessary to find out what percent of girls are 10 years old in each grade. If analysis reveals that only 50% of the girls in Grade 5 are 10 years old, and that the others range in age from 8-14 years then obviously vaccinating all the girls in Grade 5 will not achieve the programmes target and it will be very difficult to calculate any meaningful coverage rate.

However, if for an example in another country, following an assessment it is confirmed that majority of the 10 year old girls are to be found in Grade 5 – then indeed it may be operationally appropriate to select all the girls in Grade 5 for vaccination and not worry that a few who are older/younger will be vaccinated also. Overall, in this example, the target population is those girls who are 10 years old. Such an approach would need to assure that school enrolment levels were sufficiently high that there were not a lot of 10 year old “out of school” girls who would be missed. Even if the numbers are small, complementary strategies to reach and vaccinate out of school girls are required.
Box 3. A word on using a single school grade/class as a “proxy” for the target for HPV vaccination (e.g. all girls enrolled in primary school Grade/Class 5) (continued…)

With a grade based approach one needs to be careful that girls in the selected grade who are too young to be vaccinated are not missed the subsequent year when they will be of eligible age for vaccination but will now have moved on to a grade higher.

As illustrated in the examples above, grade-based targeting can be very tricky and requires a good deal of formative research to carefully understand the age composition of various grades. Moreover, it is likely that the age-distribution of a grade in one part of the country will differ from others (e.g. urban vs rural schools) and in fact, may change overtime as more and more girls are encouraged to attend, and remain in, school.

HOW CAN THE NUMBER OF GIRLS TO BE VACCINATED WITH HPV VACCINE BE ESTIMATED?

In order to plan, forecast vaccine supply, and be able to calculate coverage, an accurate estimate of the number of girls in the target age group is required. Ideally, countries should make this calculation using up-to-date national or local census data obtained from national statistical offices.

If such census data are not available, are inaccurate or are out-of-date (as is often the case), it is possible to obtain single age annual population estimates for females (and also males) by country from the United Nations Population Division website. These data are revised every two years.

See Annex 1 for an example of how to access this UNPop data file for females.

WHO will be using these UN Population Division estimates by single year of age to calculate future WHO-UNICEF estimates of national immunization coverage (WUENIC) for HPV vaccine by country and globally.

To make access and use of the UN Population Division data easier for countries and partners, WHO has extracted the population estimates for every country by year, sex and single year of age for the years 2010-2020 specifically for the 9-13 year old population. These data may be used freely and are available from the WHO website. They will be updated every two years when UNPop Division publishes its revision.

The data are in an Excel interactive pivot table database which may be accessed in English, French or Spanish and allows users to select the country and specific single-year-of-age target population(s) that have been chosen for HPV vaccination. Population estimates for boys are also provided to facilitate planning for the delivery of adjunct health interventions to all adolescents (males and females) as part of integrated approaches to adolescent and school health service delivery.

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3 http://esa.un.org/unpd/wpp/Excel-Data/population.htm
4 The next revision will extract population estimates for the 9-14 year old population, in line with the updated recommended target age range.
WHERE CAN YOU FIND THE GIRLS TARGETED FOR HPV VACCINATION?

Once the target population and its size has been determined, it is necessary to understand where the girls may be located in order to plan an appropriate delivery strategy. Girls who are attending school may be found at schools; however, not all girls attend school. Out of school girls may be dispersed and difficult to locate. They may be in the formal or informal labour market, assisting families with agriculture, household chores, tending livestock, or other activities in the community. Reaching girls who are members of pastoralist communities or live in remote locations may require specific strategies.

Countries are encouraged to work with education, census, labour, school health and other sectors to map the situation in their country, including estimations of the proportion of girls attending / not attending schools in all districts. Consultation with district leaders in a variety of geographic settings may also yield useful information about the local situation where girls of the target age range of 9-14 years old may be found. Recent experiences by the EPI programme in organizing vaccination campaigns targeting older children, such as Meningitis A or measles, may provide additional insight into ways to access young adolescent girls.

HOW MUCH WILL IT COST TO INTRODUCE HPV VACCINE?

Adding HPV vaccine to the national immunization programme will have cost implications (see previous section on financial sustainability and Box 2 on Costs page 18).

The immunization programme budget and financing plan will need to be updated. WHO has developed and field-tested a Cervical Cancer Prevention and Control Costing (C4P) Tool (see Key Resource page 17) to assist countries in determining actual costs and making five-year projections of both financial and economic costs for HPV vaccine introduction.

For more information on country experiences regarding HPV vaccine costing, financing and sustainability see companion document Scaling-up HPV Vaccine Introduction (WHO, 2016).
Box 4: Possible costs to include when budgeting for HPV vaccine introduction

- Procurement of vaccine, injection materials, and safety boxes.
- Training of all relevant health workers at all levels.
- Orientation to school staff, if vaccinations will occur at schools.
- Increased frequency of health workers leaving post for delivery through outreach.
- Expansion of the cold chain, dry storage, vaccine transport systems.
- Extra fuel expenses for cold chain and transport.
- Possible additional health personnel costs for outreach, mobile units, school delivery.
- Repairs, expansion or addition of waste management facilities to handle the additional waste generated.
- Development of materials for community sensitization and mobilization.
- Implementing comprehensive community sensitization and mobilization activities.
- Advocacy activities with key stakeholders at national, subnational, and district levels.
- Revision and printing of standard immunization forms, such as vaccination cards, tally sheets, registers, monitoring forms, guidelines, etc.
- Strengthening AEFI surveillance, reporting, and management.

HOW TO COORDINATE WITH OTHER STAKEHOLDERS?

Because HPV vaccine introduction should be a part of a comprehensive and integrated health strategy to prevent cervical cancer, it is important that the efforts of the EPI programme are closely coordinated with other stakeholders. Involvement of women’s health, cancer control, school health, adolescent health, sexual and reproductive health, non-communicable disease control, Ministry of Education, and other groups has advantages in building a strong advocacy network for achievement of a shared goal. However, collaborating with cancer control or women’s health or the Ministry of Education may be new for many national immunization programmes.

Other stakeholders who may influence the environment of support for HPV vaccine introduction may include medical and nursing associations, women’s rights and gender equity advocates, civil society organizations, government officials, parliamentarians, and even the media. Countries need to carefully consider which stakeholders are critical and supportive of HPV vaccines as a viable mechanism for cervical cancer prevention. It is also necessary to distinguish between those stakeholders/partners to be engaged in decision-making and planning, from those needed for advocacy and community engagement.

HPV vaccination targets adolescent girls. Therefore it can use platforms that may exist in countries for the delivery of other interventions for adolescent health, such as for example deworming, micronutrient supplementation, health promotion or health screening activities. These activities may be implemented through comprehensive school health or adolescent health programmes, or by programmes that focus on specific diseases such as neglected tropical diseases in the case of deworming.
HPV vaccination may provide an opportunity to deliver or expand the coverage of other adolescent health interventions. Conversely, existing programmes such as the regular distribution of deworming pills or Iron Folic Acid supplements may be opportunities to efficiently co-deliver the HPV vaccine.

Generally, convening an oversight committee (such as the Inter-Agency Coordinating Committee – ICC) has proven to be an effective mechanism to coordinate and collaborate with the diverse set of stakeholders who need to be engaged for successful HPV vaccine introductions. Many countries created a national level planning committee led by the Ministry of Health/EPI in close coordination with the Ministry of Education (for school-based delivery). Creating a series of sub-committees for activities such as Communications, Training, Vaccine Management and Logistics, and Monitoring and Evaluation, and holding regular meetings of these committees (e.g. weekly) helps to keep work-plans on track.

See Key Resource page 20 "Options for linking health interventions for adolescents with HPV vaccination. www.who.int/immunization/diseases/hpv/linking_h_interventions/en/
4. VACCINE MANAGEMENT
INTRODUCING HPV VACCINE

HOW TO FORECAST AND CALCULATE VACCINE SUPPLY NEEDED FOR HPV VACCINE?

In general, HPV vaccine introduction should follow the standard procedures for calculating vaccine supply of other vaccines and be integrated into existing mechanisms to order other vaccines. HPV vaccine should also be integrated into the stock-management system and vaccine orders must be timed such that the supply is not disrupted.

Doses required for the annual supply is based on the size of the target population, estimates of vaccine coverage of the first dose, and vaccine wastage. The simple formula below can assist:

\[
\text{Estimated size of target population} \times \text{Estimated vaccine coverage for dose 1}^* \times \text{Number of doses per schedule} \times \text{Wastage factor}^\dagger = \text{HPV vaccine doses required}
\]

* Estimated vaccine coverage for dose 1 assumes no drop-out between dose 1 and dose 2.
† Wastage factor must be adjusted for 1-dose or 2-dose vials.

WHAT COLD CHAIN CAPACITY WILL BE REQUIRED FOR HPV VACCINE?

The presentations available for each HPV vaccine are listed in the table below.

Table 4. Summary of HPV vaccine packaging and presentations

<table>
<thead>
<tr>
<th>ATTRIBUTES</th>
<th>BIVALENT (CERVARIX®)</th>
<th>QUADRIVALENT (GARDASIL®/SILGARD®)</th>
<th>9-VALENT (GARDASIL 9®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine picture</td>
<td><img src="image" alt="Cervarix" /></td>
<td><img src="image" alt="Gardasil SILGARD" /></td>
<td><img src="image" alt="Gardasil 9" /></td>
</tr>
<tr>
<td>Presentation</td>
<td>Liquid, 1-dose and 2 dose vials</td>
<td>Liquid, 1 dose vial</td>
<td>Liquid, 1 dose vial</td>
</tr>
<tr>
<td>Preservative</td>
<td>No preservative for either presentation</td>
<td>No preservative</td>
<td>No preservative</td>
</tr>
</tbody>
</table>
INTRODUCING HPV VACCINE

<table>
<thead>
<tr>
<th>ATTRIBUTES</th>
<th>BIVALENT (CERVARIX®)</th>
<th>QUADRIVALENT (GARDASIL®/SILGARD®)</th>
<th>9-VALENT (GARDASIL 9®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packaging for cold chain</td>
<td>1 dose vial, box of 1:</td>
<td>2 dose vial, box of 1:</td>
<td>1 dose vial, box of 1:</td>
</tr>
<tr>
<td>volume</td>
<td>57.7 cm³/dose</td>
<td>28.8 cm³/dose</td>
<td>75.0 cm³/dose</td>
</tr>
<tr>
<td></td>
<td>1 dose vial, box of 10:</td>
<td>2 dose vial, box of 10:</td>
<td>1 dose vial, box of 10:</td>
</tr>
<tr>
<td></td>
<td>11.5 cm³/dose</td>
<td>5.7 cm³/dose</td>
<td>15.0 cm³/dose</td>
</tr>
<tr>
<td></td>
<td>1 dose vial, box of 100:</td>
<td>2 dose vial, box of 100:</td>
<td>4.8 cm³/dose</td>
</tr>
<tr>
<td></td>
<td>9.7 cm³/dose</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Storage requirements
- Kept at 2°-8° C
- Should not be frozen
- Protected from light
- Kept at 2°-8° C
- Should not be frozen
- Protected from light
- Licenced for use in CTC (up to 3 days, up to 42°)

Shelf life
- 1 dose vials: 48 months at 2°-8° C
- 2 dose vials: 36 months at 2°-8° C
- 36 months at 2°-8° C
- 36 months at 2°-8° C

VVM
- Type 30
- Type 30
- TBD

Wastage rate
- 1-dose vials: <5%
- 2-dose vials: 10%
- 1-dose vials: <5%
- 1-dose vials: <5%

Wastage factors
- 1.05
- 1.10
- 1.05
- 1.05

Additional information on the different HPV vaccines is available on the WHO website at http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html.

Adequate refrigerator space must be available for storage of vaccines at +2 to +8° C. The WHO Vaccine Volume Calculator tool is available to help assist in calculation of cold chain capacity requirements for the amount of vaccine needed. Adequate dry storage will also need to be available for the additional injection materials, such as syringes, and safety boxes that will be needed for delivery of HPV vaccines.

HOW SHOULD HPV VACCINES BE STORED AND HANDLED?

HPV VACCINE STORAGE

HPV vaccine management should follow the same procedures as for other vaccines in the cold chain. Upon receipt and confirmation of quantity delivered, the vaccines should be placed in designated refrigerators. All HPV vaccines should be stored between +2° to +8° C.

INTRODUCING HPV VACCINE

HPV vaccines SHOULD NOT BE FROZEN as they are exceptionally sensitive to temperatures lower than +2°C and lose efficacy if frozen. Vaccines subjected to temperatures lower than +2°C should not be used. If there is suspicion that a vaccine has been frozen, a shake test should be performed. Annex 2 provides the WHO protocol for a shake test.

HPV vaccines cannot be placed directly on or near the freezer portion of refrigerators, and HPV vaccines should not be stored near the liners or walls of cold boxes and or ice-packs in vaccine carriers. Proper procedures for conditioning ice-packs in vaccine carriers or use of cold packs in vaccine carriers should be followed. WHO guidance on these procedures is available in the following documents: Immunization In Practice: A Practical Guide for Health Staff, Module 2 – The Vaccine Cold Chain² and the WHO Vaccine Management Handbook modules³.

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

Under special conditions, some HPV vaccine products are licenced for Controlled Temperature Chain (CTC) which permits the vaccine to be kept at ambient temperatures not exceeding 42°C for up to 72 hours (See Box 1 page 6 for details).

HPV VACCINE HANDLING

For use of 2-dose vials of bivalent HPV vaccine, countries should ensure that health workers are trained on appropriate handling of unpreserved multi-dose vials, per the guidelines set out in the WHO multi-dose vial policy⁴ (see Box 5).

Opened vials of the product should be discarded at the end of the immunization session or after 6 hours, whichever comes first. Each vial contains a vaccine vial monitor (VVM) to indicate cumulative exposure to heat. The VVM provides a warning when the vaccine is likely to have been degraded and should be discarded. Both HPV vaccines have been certified for VVM type 30. It is important to highlight that the VVM does NOT alert about vaccine freezing.

² http://www.who.int/immunization/documents/IIP2015_Module2.pdf
Box 5: WHO requirements for 2-dose presentation of preservative-free Cervarix™*

Special attention to training of health care staff will be required for the proper use of the Cervarix™ two-dose presentation because it is a multi-dose preservative-free vaccine. Specific pre-introduction measures are required to assure programmatic readiness is achieved prior to introduction.

To mitigate against potential programmatic risk countries should ensure that they:

- Understand the benefits and potential contamination risks of the two-dose unpreserved presentation and understand the need for special training and good supervision to enhance immunization worker practices.
- Conduct post introduction evaluations to determine levels of Health Care Worker knowledge and compliance with the correct handling of the vaccine; and implement corrective training if needed.

Prior to introduction and before UNICEF Supply Division will ship the vaccine countries must:

- Ensure training materials are in place in immunization centres prior to the launch of the vaccine.
- Place stickers on refrigerators at all levels indicating that opened vials of the vaccine must be discarded six hours after opening. The stickers should be in place prior to the launch of the vaccine.


Box 6: NEW VVM Infographic

WHO has just released a new infographic that summarises how health workers can use vaccine vial monitors (VVMs) to decide whether or not to use a vaccine vial. Most notably, it presents VVM colour change as a continuous progression, rather than as four distinct stages.

A VVM is a chemical indicator label attached to the vaccine container (vial, ampoule or dropper) by the vaccine manufacturer. As the container moves through the supply chain, the VVM records its cumulative heat exposure through a gradual change in colour. If the colour of the inner square is the same colour or darker than the outer circle, the vaccine has been exposed to too much heat and should be discarded.

The main purpose of VVMs is to ensure that heat-damaged vaccines are not administered. The VVM status is also used to decide which vaccines can safely be kept after a cold chain break occurs thus minimizing unnecessary vaccine wastage. In addition, VVM status helps the user decide which vaccine should be used first – a batch of vaccine showing significant heat exposure should be distributed and used before a batch that shows lower heat exposure, even if its expiry date is longer.
Box 6: NEW VVM Infographic (continued…)

Please use the new infographic in guidance and training materials, and share widely. The infographic is available in English and French on the WHO website:


Vaccine Vial Monitors

The color of the inner square of the VVMs begins with a shade that is lighter than the outer circle and continues to darken with time and/or exposure to heat.

- **USE**
  - Square is lighter than outer circle
  - The color of the inner square of the VVMs begins with a shade that is lighter than the outer circle and continues to darken with time and/or exposure to heat.

- **DO NOT USE**
  - Square matches circle
  - Square is darker than circle
  - Once a vaccine has reached or exceeded the discard point, the colour of the inner square will be the same colour or darker than the outer circle.

Inform your supervisor

Cumulative heat exposure over time

WHAT IMPACT WILL HPV VACCINE INTRODUCTION HAVE ON WASTE MANAGEMENT?

As with any new vaccine introduction, HPV vaccine introduction will generate additional vaccine waste that requires appropriate disposal. All current waste management facilities should be reviewed to ensure there is adequate capacity to handle increased waste volume generated by HPV vaccine delivery.

The impact on the waste management system will depend on the delivery strategy. It is likely to be greater if HPV vaccine is delivered in a campaign-style twice a year, than for continuous delivery of HPV vaccine at health centres throughout the year, which will increase the waste volume but in a more stable manner. Countries should carefully plan for the frequency and amount of increased waste.
5. MICROPLANNING AT THE DISTRICT LEVEL
Adequate microplanning at the district level prior to introduction is essential. In particular, for HPV vaccine delivery there are a few issues that need careful consideration.

**VERIFYING THE ESTIMATED TARGET POPULATION**

Estimates of the target population will have most likely been made using national or subnational data extrapolated from the last census. Because population movements can be significant and local circumstances may have changed, it is important to verify estimates of the eligible population at the district level for each district in the country. This is sometimes referred to as enumeration.

District health and education leaders should be involved, especially if schools will be a part of the vaccine delivery strategy. Checking for new schools that have opened or schools that have closed may also have an impact on the overall estimates of the eligible population in the district.

For enumeration for school-based strategies, the following steps are suggested:

• Generate an up-to-date list of all schools in the district (including private schools and special education schools which may be missing from official lists).
• Contact the schools and obtain the number of target girls who are enrolled.
• If possible, have the school pre-register or enumerate the girls who are to be vaccinated and provide a list of the girl’s names and dates of birth to the health facility.
• Confirm with the schools and obtain agreement that the dates proposed for vaccination are convenient and do not conflict with school exams or holiday periods.

For enumeration for community outreach strategies:

• Involve volunteer health workers and community members to generate up-to-date lists of girls of eligible age who do not attend school.

Naturally occurring events, such as agriculture migration or natural disasters, could also influence population estimates. Seasonality could also be a factor if populations move when vaccinations are scheduled in local areas. Planning for these known seasonal migration patterns can help ensure more accurate projections of the number of eligible girls who may be available for vaccination. Conflict, famine, and political stability may also be localized events impacting the movement of people. Understanding if this situation is present can help inform the estimates of the target population as well.

**ENSURING THAT COLD CHAIN CAPACITY IS ADEQUATE**

Management of HPV vaccine in local health centres should follow the same procedures as is done for any vaccine requiring continuous cold chain. A quality and recent effective vaccine management (EVM) assessment can inform if any health facilities require cold chain expansion, maintenance or strengthening in advance of HPV vaccine introduction. Similarly, it will be necessary to ensure that the health facility has sufficient vaccine carriers and cold-packs if HPV vaccination will be conducted via outreach to schools and communities. Transportation costs and per diems also need to be included.

Vaccine logistics will be impacted by the chosen delivery approach. Offering HPV vaccine throughout the year alongside routine infant vaccinations will have different implications for the logistics, forecasting and supply than providing HPV vaccine only periodically (e.g. once or twice a year). The microplanning process needs to consider this when preparing health facilities for HPV vaccine introduction.
PLANNING AND COORDINATING LOGISTICS FOR VACCINE DELIVERY AT OUTREACH LOCATIONS IN SCHOOLS AND COMMUNITIES

Logistics for vaccinations at outreach locations or at schools requires careful planning and advanced coordination to ensure efficient implementation, as health workers will be leaving the health post. See Box 7 below for a microplanning checklist for HPV vaccination outreach sessions.

Box 7. Microplanning checklist for HPV vaccine delivery at schools and outreach locations

- Vaccine delivery outside of health centres may result in additional costs. These costs should be planned for and secured prior to delivery.
- Ensure that the human resources needed to carry out the outreach are arranged without disrupting services at the health centre.
- Map all health centres and health posts in the district and all schools and outreach locations to be reached.
- Coordinate with district education officials to ensure all schools are accounted for in the mapping exercise.
- Try to arrange HPV vaccination at schools and outreach locations to be conducted by the nearest health facility/post in that catchment area. This helps to reduce transportation costs, shortens the distance to carry vaccines and supplies, and supports building positive relations between the local staff at health centres with the surrounding community.
- Assess opportunities to combine HPV vaccination outreach with other outreach activities for integrated delivery with other health interventions.
- Coordinate closely with school administration, headmasters, and education officials to set dates for vaccination that do not conflict with school exams and holidays and which reduce disruption to regular classes.
- Pay particular attention to private schools, religious and other schools that are not part of the public school network.
- Make sure that parents/communities are informed in advance that HPV vaccination will take place, and that consent is given (see section below for consent options).
- If an entire group of girls is to be vaccinated at once, the time needed for one health worker to vaccinate twenty girls is approximately one hour.
- Districts should consider utilizing more health workers at larger schools or outreach sessions to ensure all girls mobilized for vaccination can be accommodated in a single session.
- Repeated visits to schools or outreach locations for girls missed should be balanced against time and financial resources required and available with the number of girls that may possibly be reached.
- If good defaulter records are maintained, missed girls can be told to come to the health centre or next outreach session to catch up their vaccination, or they can be vaccinated the next time the health team goes to the school.
- Important strategies for missed girls include encouraging teachers to refer girls to the nearest health centre/outreach, reminder text messages to parents or guardians, and community announcements for vaccination days that will include HPV vaccine.
CONSENT FOR VACCINATION

Consent processes for vaccination should be reviewed and determined by countries in accordance to national EPI policies. Specific policies and procedures for obtaining individual informed consent for HPV vaccines will need to consider local infrastructure and resources. For HPV vaccines, some countries have found that the introduction of a new or different consent procedure has led to suspicion that the HPV vaccine is experimental or risky. Therefore, the consent process needs to be carefully planned and implemented.

Consent procedures vary by country, and can include:

- formal, written consent (e.g. the caregiver signs a form either giving permission or refusing for vaccination of the child)
- verbal consent
- implied consent

As described previously (Key Resource page 21) WHO has developed a short resource document on consent approaches for vaccination of older children.¹

When vaccination is carried out in schools, local or national school authorities normally authorize the intervention to take place at their premises. This authorization is needed for planning and implementing the vaccination sessions in schools. The same applies when community or traditional leaders are asked for permission for vaccination to be carried out in their communities. This authorization, however, does not imply informed consent by the individuals in that school or community. In a legal sense, school or local welfare or other community authorities do not have the capacity to consent to medical interventions on behalf of the children in their care. Exceptions, stipulated in local laws and regulations, may exist in defined, special situations.

When mandatory vaccination is established in relevant provisions in law, consent may not be required. If the mandatory nature of vaccination is based on policy, or other forms of soft law, informed consent needs to be obtained. Some countries allow individuals to express non-consent (opt-out) and obtain an exemption for mandatory vaccines.

For childhood vaccination, parental consent can be implied when a parent voluntarily brings the child to be vaccinated at a health clinic. However, older girls may not be accompanied by parents at the time of HPV vaccination, regardless of location. In these situations, implicit parental consent cannot be as easily assumed, and explicit written or verbal consent may require additional steps. Any explicit consenting or authorization process needs to be accounted for in the microplan and timeline established for HPV vaccine introduction.

Regardless of a country’s informed consent policy, information and education to girls, their parents, teachers and the community should be given to allow understanding of the benefits and risks of HPV vaccination and to ensure acceptance. Effective communication strategies are described in the next chapter on communication and social mobilization.

¹ www.who.int/immunization/programmes_systems/policies_strategies/consent_note/en/
6. COMMUNICATION AND SOCIAL MOBILIZATION
DEVELOPING A COMMUNICATION PLAN

Increasing community awareness through timely, complete and appropriate communication is the key to successful and sustainable HPV vaccine introduction.

A comprehensive guide entitled *HPV vaccine communication: special considerations for a unique vaccine* (see Key Resource below) has been developed by WHO to assist countries to implement an effective communication strategy for sensitization and mobilization to improve HPV vaccine uptake. The introduction and continued delivery of any new vaccine requires a communication plan. Countries are encouraged to refer to this guide for detailed advice.

The basic elements of a communication plan include the following:

1. A communications team
2. Technical programme objective
3. Situation analysis
4. SMART\(^1\) communication objectives
5. Target audiences
6. Messages for each audience
7. Strategies, activities, and channels to reach audiences
8. Branded materials
9. A crisis communication plan
10. Monitoring and evaluation plan
11. Work plan with budget (revised as required)

**KEY RESOURCE**

*HPV Vaccine Communication: Special considerations for a unique vaccine (updated in 2016)*

Communication is a key component of any successful public health programme, and an investment in communication for HPV vaccine is particularly important, given its unique qualities.

This document offers guidance in three main areas: (i) advice on basic communication planning and implementation for immunization; (ii) specific considerations for HPV vaccine; and (iii) crisis communication. It draws on the experiences from countries that have either introduced the vaccine nationally or conducted demonstration projects. It includes advice about cross-sectoral advocacy, team building and formative research; a description of the recommended target groups; the importance of careful planning so that communication reaches hard-to-reach girls; and advice on effective messaging, materials and channels.


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\(^1\) SMART Objectives are Specific, Measurable, Achievable, Relevant and Time bound.
DEVELOPING KEY MESSAGES FOR HPV VACCINES

Creating effective messages is not easy. Accurate, technical, culturally appropriate, practical and motivational information must be conveyed in a way that can be easily understood by the different audiences at different times. The level of detail presented must be appropriate for each audience: girls, parents, teachers, health workers, and the wider community. Messages should be clear, simple and accurate. The actual wording of messages should consider culture, language, and literacy, and ensure a call to action.

Experience with HPV vaccine to date has provided some evidence about effective messaging. However each country is unique, and formative research, including focus group discussions and key informant interviews, may be needed to develop and test messages about HPV vaccination. Such exercises are part of the community engagement process and signal genuine care about addressing the views of target groups. For HPV vaccine, research can also help to pinpoint colloquial language; culturally-appropriate language and terminology for sometimes sensitive areas such as sexual behaviour and anatomy; and for preferred, trusted information sources and channels (e.g. public announcements, use of mobile phone text messaging (SMS) or social media).

Box 8. Examples of key messages for HPV vaccine acceptability

- HPV vaccine for young girls protects them from cervical cancer later in life when they are grown women with families of their own.
- Cervical cancer affects the reproductive organs of women and is a leading cause of death among women of child bearing age.
- Girls should be vaccinated when they are young before exposure to HPV.
- You can protect your daughter and her future by getting her vaccinated.
- The vaccine is safe, causes no major side-effects, and will not harm a girl’s ability to have children in the future.
- HPV vaccine is available free-of-charge at (location) (date, time).
- Most girls should be vaccinated twice, with 6 months (or indicate chosen schedule) between doses.
- The government supports HPV vaccination and has added it to the national immunization programme.

IDENTIFYING THE AUDIENCES

Because HPV vaccine will be new, targeting an age group not normally included in the EPI schedule, and could have some potential sensitivities, it is important that communication messages reach every group that will have an interest in the vaccine. Each audience should be mapped out, and each will require specific messages – some requiring more information than others. For example, depending on literacy and culture, girls and their parents will require basic information about the vaccine, vaccination programme and schedule, using simple easy-to-understand language. However,
others in the community such as community and religious leaders, government officials, and health and education authorities may need more targeted messages to foster their understanding of the programme, the government’s rationale for including HPV vaccine in the national immunization schedule, the vaccine safety and the benefit for girls.

School headmasters and teachers are also an important audience, especially if they have an active role in supporting vaccinations at school. Health workers will require the most detailed information as they may need to be convinced about the importance of HPV vaccine, and need to provide information and answer questions from parents, girls, and the community, as well as for their own understanding to be able to answer questions they may receive.

Professional organizations, cultural and religious organizations, politicians, and the media are also important audiences as they need to support vaccination of their communities.

**USING MULTIPLE CHANNELS AND OPPORTUNITIES FOR COMMUNICATION**

It’s important to use multiple channels to provide and reinforce messages.

Country experience has shown that parents’ decisions are heavily influenced by receiving information from sources they trust - principally their families and close friends, local health workers, their teachers and religious leaders. Parents also like to receive information through interpersonal, direct communication and discussions.

Materials such as short “frequently asked questions” or simple brochures in locally understood languages may help reinforce verbal messages.

A variety of other activities and channels could be considered. These may include public media such as posters, billboards, and announcements in the community, at churches and mosques, or on the radio. In areas with access, television spots, mobile phone text messaging (SMS), and social media may be important and effective communication channels, particularly for young people.

A country example showing the range of communication activities used for HPV vaccination is presented below (see Table 5).

The timing of communication and social mobilization activities is critical to ensure there is a penetration of information to all audiences in good time prior to HPV vaccination. Each target audience may be different in the intensity and frequency required and this should be included in the communication plan. An example of the timing and frequency of HPV communication is provided in Annex 3.
## Table 5. Example of a communication plan for HPV vaccines

<table>
<thead>
<tr>
<th>AUDIENCE</th>
<th>MESSAGES</th>
<th>DELIVERED BY</th>
<th>ACTIVITIES</th>
<th>MATERIALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible girls</td>
<td>Basic facts about cervical cancer</td>
<td>Sub-county supervisors</td>
<td>Sensitization meeting</td>
<td>HPV leaflet</td>
</tr>
<tr>
<td></td>
<td>Basic facts about the preventive HPV vaccine</td>
<td>Health workers</td>
<td>Distributing materials</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Benefits of being vaccinated</td>
<td>Teachers</td>
<td>Radio messages</td>
<td></td>
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<tr>
<td></td>
<td>Their role in HPV vaccination</td>
<td>Parents</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Mobilizers</td>
<td></td>
<td></td>
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<tr>
<td>Parents</td>
<td>Facts about cervical cancer and prevention</td>
<td>District Health Team</td>
<td>Orientation sessions</td>
<td>HPV leaflet</td>
</tr>
<tr>
<td></td>
<td>Availability of preventive vaccine</td>
<td>Sub-county supervisors</td>
<td>Distributing materials</td>
<td>Radio messages</td>
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<td></td>
<td>Facts about the vaccine</td>
<td>Health workers</td>
<td>Radio messages</td>
<td>Publish information in local media</td>
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<td></td>
<td>Age-appropriate ways to discuss cervical cancer with children</td>
<td>Teachers</td>
<td></td>
<td>Community film shows</td>
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<tr>
<td></td>
<td>Their role &amp; responsibility</td>
<td>Mobilizers</td>
<td></td>
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<tr>
<td>School administration, School management and teachers</td>
<td>Facts about cervical cancer and prevention</td>
<td>District Health Team</td>
<td>Orientation sessions</td>
<td>HPV leaflet</td>
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<td></td>
<td>Availability of preventive vaccine</td>
<td>School Management</td>
<td>Distributing materials</td>
<td>HPV guidebook</td>
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<td></td>
<td>Facts about the vaccine</td>
<td>Sub-county supervisors</td>
<td>Radio messages</td>
<td>Radio messages</td>
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<tr>
<td></td>
<td>Age-appropriate approaches to addressing cervical cancer with children</td>
<td>Health workers</td>
<td>Publish information in local media</td>
<td>Articles in local media</td>
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<tr>
<td></td>
<td>Their roles &amp; responsibilities</td>
<td></td>
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<tr>
<td>Community leaders</td>
<td>Burden of disease</td>
<td>District Health Team</td>
<td>Orientation sessions</td>
<td>HPV leaflet</td>
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<td></td>
<td>Importance and benefits of prevention</td>
<td>Sub-county supervisors</td>
<td>Distributing materials</td>
<td>HPV guide</td>
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<td>Availability of preventive vaccine</td>
<td>Health workers</td>
<td>Radio messages</td>
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<td>Facts about the vaccine</td>
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<td>Publish information in local media</td>
<td>Articles in local media</td>
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<td></td>
<td>Key messages to help dispel misinformation</td>
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<td>Their roles &amp; responsibilities</td>
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RUMOURS AND CRISIS MANAGEMENT

Experience with HPV vaccine shows that communication crises are fairly common – and often due to rumours and misinformation. A good communication plan can avert these problems, and also help to manage them if a crisis emerges.

While HPV vaccines have an excellent safety profile, experience from some countries indicate that misperceptions about HPV vaccine risks can have serious consequences, and in some cases, has led to a complete halt to all HPV vaccination activities in the public sector.

Countries should ensure clear communication about the safety and common side effects of the vaccine, together with endorsement from trusted leaders. Communication helps build trust with the public. This involves including information on possible side effects in any education material or messaging used when communicating with parents and the community. Awareness among health workers and the public of possible adverse events will also reduce fear and misunderstanding and facilitate early recognition and treatment of side effects. It is very important to engage the media (through journalist briefings, information packages, etc.) prior to HPV vaccination, because if they are not well informed about the facts media can often amplify any rumours, leading to a larger crisis.

Countries should prepare a crisis communications plan to allow for a rapid effective response to AEFIs, anti-vaccine movements, and any allegation that can have a negative effect on public acceptance of HPV vaccines and trust in the immunization programme. Countries should have in place the basic elements of a crisis plan, which may include:

- An AEFI committee at different levels which can meet immediately to discuss an action plan;
- Identified, well-respected spokespersons at all levels;
- Clear channels of communication with various media;
- Engaging with credible opinion and traditional leaders to address misconceptions and rumours;
- Training of health workers on how to communicate with the public about AEFIs and safety concerns; and
- An AEFI action plan with specific roles for immunization programme partners.

WHO’s document *HPV Vaccine Communication: Special Considerations for a unique vaccine* has been updated in 2016 to include the latest information and global experiences with managing HPV vaccine communication crises. See additional Key Resources below.
KEY RESOURCES

WHO On-line e-Learning Course in Vaccine Safety

WHO’s Global Vaccine Safety group has developed an online e-learning course on Vaccine Safety basics to help health workers understand the origin and nature of adverse events, the importance of pharmacovigilance, and risk and crisis communication.

The content of this course has been compiled by international vaccine experts committed to the promotion of best practice in the implementation of immunization programmes worldwide. It includes a case-study on how a potential HPV vaccine crisis was averted (http://vaccine-safety-training.org/c-introduction.html).

For those who do not have constant internet access the e-learning course is available as a CD-ROM or downloadable PDF.

http://vaccine-safety-training.org/home.html

Vaccine Safety Events: Managing the Communication Response

This manual developed by WHO’s European Regional Office provides practical, informative strategies and tools to help plan and manage a communications response following a vaccine-related event in your local community, at a national level, or beyond. By reading this manual, you will learn how to use communications strategies and tools to increase public trust and confidence in vaccines, and to minimize the negative impact of any vaccine-related event.

Box 9. Summary: Communication planning and considerations for HPV vaccine*

Communication is:

- **A process.** People need time to change behaviours – to learn, absorb and confirm information, make a decision to act on it and encourage others to do the same.
- **About community engagement.** It’s a conversation and not a lecture.
- **About equity** with plans to engage hard-to-reach populations.
- **An investment.** Effective communication activities will cost money and time. The return on investment is improved immunization coverage and better health for girls and women.
- **Imperfect.** Communication involves human beings, and we cannot predict what people will think or do in every situation.

HPV vaccine is different:

- **Start early.** Early planning can lead to on-time implementation. Begin communicating with communities about a month before the vaccine is introduced.
- **Build a cross-sectoral team.** HPV vaccine introduction involves immunization, education, cancer, sexual and reproductive health, adolescent health, youth, professional associations and other key members of civil society.
- **Conduct a situation analysis** including formative research if necessary. It’s important to understand how different audiences understand and will respond to HPV vaccine.
- **Plan for a multi-year effort.** It will take time for HPV vaccine to “settle” in and be accepted as a part of a routine programme.
- **There will be concerns.** HPV vaccine is new in the country; it is targeted at adolescent girls; it may not seem like a priority, and there may be rumours about whether it’s a “trial”, its safety and about fertility.
- **Government endorsement is important for a successful programme.**
- **Identify and engage all groups that may have concerns.** Ensure advocacy plans for them.
- **Understand and plan for hard-to-reach girls.** Who and where are these girls? In the future, they may have the least access to cervical cancer screening even when it’s available in the country.
- **Interpersonal communication from trusted influencers can have the most impact.** Train health workers and teachers to communicate effectively about HPV vaccine and ensure religious and community leaders understand and know how to promote it.
- **The first year will have some challenges.** It’s a new programme and there will be bumps but...
- **High coverage can be achieved.** HPV vaccine will save lives. Communication has been key to high coverage in countries with successful programmes.

*From: HPV Vaccine Communication: Special considerations for a unique vaccine, WHO, updated 2016*
7. IMPLEMENTATION – TRAINING, SERVICE DELIVERY AND SUPERVISION
INTRODUCING HPV VACCINE

TRAINING

Even though many aspects of HPV vaccine delivery are the same as for other established routine immunizations, health staff will need to receive specific training before implementing HPV vaccination. If prepared well, a two-day training should be sufficient to cover the necessary background information, operational issues and hands-on practice. Ideally, the training for HPV vaccine introduction would be included as a part of any regular annual or refresher training for health workers.

Linking training with an annual microplanning activity can also build efficiencies and allow for more integrated planning of vaccine delivery, especially if schools will be used as a location for vaccinations.

In cases where schools will have a role in the introduction of HPV vaccine, teachers and headmasters may also need a brief half-day orientation training in accordance to their specific tasks. Having school staff attend the first part of a planned health worker training may help to build trust and facilitate future collaboration.

For health workers, WHO has developed a training package of slide sets consisting of seven modules which can be downloaded from the WHO web site and adapted by countries:

1. Introduction to HPV infection and cervical cancer
2. HPV vaccine attributes and storage conditions
3. HPV vaccine eligibility and contraindications
4. HPV vaccine administration
5. Recording and monitoring of HPV vaccine doses
6. Communicating about HPV with key stakeholders
7. Taking care of adolescent patients

Training materials need to be prepared (or translated) in the appropriate local language and in sufficient quantities. Summarized reference materials and job aids should be developed and given to the participants attending training so that they have information to refer to and to share with others when they return to their post. This is particularly important for cascade training.

Interactive, hands-on training, such as field visits, showing videos of correct practices, small group discussions, demonstrations and skills practices are generally more successful techniques for training adults than classroom lectures.

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1 Essential Training Package for 2-dose schedule HPV vaccine introduction: http://www.who.int/immunization/diseases/hpv/2dose_schedule/en/
Box 10. Training for HPV vaccination for health workers should include the following:

- Brief overview of cervical cancer morbidity and mortality and current strategy of the government for its prevention and control.
- Review of the rationale for adding HPV vaccine to the national immunization schedule.
- Review of all relevant policies, such as population targeted, consent requirements, multi-dose vial policy, etc.
- Detail for the HPV vaccine delivery strategy chosen, definition of the target population, location of vaccinations, and frequency of delivery.
- Key messages for girls, parents and communities and the social mobilization plan.
- Conducting well-organized and efficient immunization sessions.
- Adverse events following immunization (AEFI) – how to prevent, detect, treat, and report.
- Instruction and practice on how to administer HPV vaccine, including schedule, dosage, storing and handling the vaccine, vaccine vial monitors (VVMs), co-administration with other vaccines, safe injection, and waste management.
- Data collection, record keeping and reporting forms for doses delivered, tally sheets, vaccine register, AEFI, etc.
- If applicable, seeking opportunities to integrate HPV vaccine delivery with other health or education interventions.
- Stock management of HPV vaccine supplies, including how to forecast supplies and wastage rates.
- Monitoring and supportive supervision plans.
- Microplanning (with schools, if applicable) to ensure that all communities, especially hard to reach, have access to vaccination services.
- Elaboration of the detailed timeline/chronogram for HPV vaccine introduction.

SERVICE DELIVERY

HOW TO ORGANIZE AN HPV VACCINATION SESSION

Vaccination sessions for HPV vaccine will be similar to those organized for infant immunizations. As with other vaccines, immunization sessions for HPV vaccine should have all the necessary supplies and materials for effective delivery. Supplies include chair and table, water and soap or hand sanitizer, safety boxes with closed lids, waste bags for garbage, and information, education and communication (IEC) materials. All forms and monitoring tools should be brought to every vaccination session, including the vaccination logbook or register, tally sheets, vaccination cards, and AEFI forms in case of immediate reactions.

In addition to following all the basic requirements for any injectable vaccine, a few additional steps before and after are required to properly administer HPV vaccine.
INTRODUCING HPV VACCINE

Steps prior to HPV vaccine injection

1. Verify eligibility of the girl
2. Ensure name, address (if collected), and date of birth or age is recorded in vaccine register
3. Ensure girl understands purpose, benefit and risks of vaccination, as well as of not receiving the vaccine
4. If required, check written consent received
5. Verify girl assents to vaccination
6. Ensure no contraindications
7. Check vaccination card and determine if 1st or 2nd dose is due
8. Ensure girl is seated for vaccination
9. Administer vaccine following the procedures for safe injection (see section below)

Steps after HPV vaccine injection

1. All girls are strongly advised to rest for at least 15 minutes after vaccination, in case they experience dizziness or any immediate untoward effects
2. Document dose received and date in vaccine register and vaccination card
3. Remind girl of need and date of next dose, if applicable
4. If all doses have been completed, return completed vaccination card to the girl for safe keeping
5. Should any adverse event occur, manage, document, and report according to established national AEFI guidelines

When HPV vaccination takes place in schools, teachers may be able to assist in mobilizing girls for vaccination, checking registers for eligibility, and providing support to health workers by recording information on vaccination cards and/or registers. A classroom in the school may also be a convenient enclosed space to conduct the vaccination session while minimizing disruptions to the rest of the school. Figure 3 provides an example of the client flow for a school-based vaccination session.

PRIVACY

If possible, it may be beneficial that actual vaccination is done privately, rather than in front of the whole group of girls. Fear of pain, or instances of fainting, may affect the larger group. This can cause mass psychogenic reactions and a crisis situation against HPV vaccination. Existence of social media nowadays has led to the rapid spread of fears beyond a single vaccination site or school.

Practical suggestions to reduce fear and distress include:
• Use a screen for privacy
• Have girls wait outside the vaccination room
• Manage only small groups of girls at a time

Research studies\(^2\) have documented that fear of HPV vaccination was promoted by witnessing the fear reactions of peers; perceived judgement by peers; lack of information or misinformation; and being vaccinated later in the day. Fear was moderated by procedural factors, the support of peers, appropriate knowledge, and nurses’ distraction techniques or approach. Fear also affected acceptance of HPV vaccination.

Figure 3. Client flow for school-based vaccinations – an example

SAFE INJECTION PRACTICES

As with all other immunizations, HPV vaccine should be delivered with good technique and following the best practices for safe injections:

1. Always follow manufacturer recommendations for use, storage, and handling

2. 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

3. Wash hands with soap and water and drip dry

4. Prepare each dose immediately before administering. Do not prepare several syringes in advance

5. Check the vial for condition, VVM status, and expiry date. Do not use if the colour of the VVM’s inner square is the same colour or darker than the outer circle, or if packaging is punctured, torn, or damaged, or if vial contains particles or if there is discoloration

6. Use a new auto-disable (AD) syringe for each girl

7. Do not touch any part of the needle

8. Inject entire content of the syringe into the deltoid muscle of the upper arm using a perpendicular 90 degree angle

9. Discard the syringe and needle directly (no recapping) into a safety box immediately after administering the vaccine
10. 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 enter.

11. Do not overfill the safety box. Close the container and seal the opening when the box is ¾ full.

12. Keep safety boxes in a dry, safe place until they can be safely disposed.

13. Do not dispose of used syringe and needles in an open box or container.

**ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)**

**MONITORING**

An adverse event following immunization is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the use of the vaccine. If not rapidly and effectively dealt with, AEFIs can undermine confidence in a vaccine and ultimately have dramatic consequences for immunization coverage and disease incidence.

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, due to programmatic or human errors that compromise the vaccine quality, or allergic reactions to components in the vaccine.

AEFIs can be classified into 5 categories:

1. **Vaccine product-related reaction**
   - Caused or precipitated by inherent properties of the vaccine product.

2. **Vaccine quality defect-related reaction**
   - Caused or precipitated by a vaccine due to one or more quality defects of the vaccine product, including the administration device, as provided by the manufacturer.

3. **Immunization error-related reaction**
   - Caused by inappropriate vaccine handling, prescribing or administration and that thus, by its nature, is preventable.

4. **Immunization anxiety-related reaction**
   - Arising from anxiety about the vaccination.

5. **Coincidental event**
   - Caused by something other than the vaccine product, immunization error or immunization anxiety.

Common HPV vaccine reactions which resolve spontaneously and rarely require treatment are:

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

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, according to the established protocols of the EPI programme. Emergency kits to treat anaphylaxis should be always available when vaccination is provided.

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WHO produces a series of Information Sheets on the Observed Rate of Vaccine Reactions which are available on the web. The Information Sheet on the Observed Rate of Vaccine Reactions for HPV vaccine is provided in Annex 4.

Box 11. HPV Vaccine and the Global Advisory Committee on Vaccine Safety (GACVS)

The Global Advisory Committee on Vaccine Safety (GACVS) was established in 1999 to respond promptly, efficiently, and with scientific rigour to vaccine safety issues of potential global importance. The Committee provides independent, authoritative, scientific advice to WHO on vaccine safety issues of global or regional concern with the potential to affect in the short or long term national immunization programmes.

On a regular basis, the GACVS has systematically reviewed and investigated safety concerns raised about HPV vaccines. To date, GACVS has not found any safety issue that would alter its recommendations for the use of the vaccine.

Concerned about the persistence and public health harm caused by HPV vaccine safety issues based on anecdotal observations and reports in the absence of biological or epidemiological substantiation, in 2014 GACVS issued a statement summarizing their findings over six years. This summary statement, and all other HPV vaccine safety statements (most recent January 2016) and GACVS meeting reports are available at:

http://www.who.int/vaccine_safetycommittee/topics/hpv/en/

The GACVS continues to closely monitor the safety of HPV vaccines.

Monitoring and reporting of AEFI

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. Groups opposed to vaccines for any reason may initiate or perpetuate rumours 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 rumours and demonstrate continued safety of HPV vaccines.

A system should be in place to facilitate prompt reporting and investigation of AEFIs. The National Regulatory Authority (NRA) and the National Immunization Technical Advisory Group (NITAG) should take a proactive role in investigation of reports of serious adverse events to verify any link to HPV vaccine and develop communication messages to address rumours. Clear procedures for what should be reported and how are necessary elements of any AEFI reporting system. Health workers should be trained on the recognition of adverse events, completion of the AEFI reporting form, and appropriate notification of supervisors and the district health officer, according to established protocols. Countries should ensure that HPV vaccine adverse event monitoring is fully incorporated within the national AEFI guidelines prior to national introduction.

Annex 5 provides an example of an AEFI reporting form for HPV vaccine that can be adapted for country context as well as a generic reporting flow for the AEFI reporting form once completed.

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4 http://www.who.int/vaccine_safetyinitiative/tools/vaccinfosheets/en/
The WHO Aid memoire for AEFI Investigation and a sample AEFI investigation form can be found in Annex 6.

Detailed procedures for reporting AEFIs are described in the WHO Global manual on surveillance of adverse events following immunization, 2014. 5

**SUPPORTIVE SUPERVISION**

Once HPV vaccine is introduced, implementation should be periodically monitored through supportive supervision, which includes “on-the-job” training. Supportive supervision strengthens the capacities of health workers and improves performance; visits can be used to provide feedback, update health staff on this and other vaccinations, enhance motivation, and identify training needs.

Supervisor schedules and integrated checklist tools should be adapted to include HPV vaccine. Staff should be specifically asked about HPV vaccine coverage and any problems (supply or demand) that they face with this vaccine. Managers can refer to WHO’s Training for Mid-Level Managers (MLM): Module 4 - Supportive Supervision6 to develop effective supportive supervision programmes and for a sample supervisory checklist that can be adapted to include HPV vaccine.

**Box 12. Supportive supervision:**

- Encourages open, two-way communication;
- Builds team approaches that facilitate problem solving;
- Focuses on monitoring performance towards goals;
- Uses data for decision-making;
- Depends on regular follow-up with staff to ensure that new tasks are being implemented correctly.

*Supportive supervision is helping to make things work, rather than checking to see what is wrong.*

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8. MONITORING AND EVALUATION
MONITORING TOOLS

The main recording and reporting tools that are used for immunization should be adapted to include HPV vaccine. These are:

- Immunization register
- Tally sheet
- Immunization card (Home-based Record)
- Defaulter tracking system
- Stock record
- Integrated monthly report

This chapter provides brief highlights. More general information can be found in WHO’s *Immunization in Practice: A Practical Guide for Health Staff, Module 6 – Monitoring and Surveillance*, 2015¹.

Specifically for HPV vaccine, WHO has also developed a new resource -- *HPV Vaccine Coverage Monitoring Tool*² which explains in detail, according to different delivery strategies, how HPV vaccine recording and monitoring tools can be adapted. It includes examples of standardized forms and tables for all levels (service delivery, district, and national).

IMMUNIZATION REGISTERS

Immunization registers record doses given to an individual and helps health workers keep track of each dose that has been administered and the completion of the vaccination series. The immunization register is the basis for tracking individual immunization status (should for example, the vaccination card be lost) and for tracking defaulters.

Depending on the HPV vaccination delivery strategy that is being used it may not always be possible to take the immunization register away from the health facility. In these circumstances it may be helpful to develop a separate HPV vaccination register or defaulter tracking system using duplicate vaccination cards, or use temporary register sheets which can be copied back into the main register after the outreach has been completed.

Each dose of HPV vaccine delivered to every eligible girl should be recorded against their name in the register. When used effectively and the records are organized in manner that facilitates identifying particular children, registers can be an additional tool for health workers to be aware of who has missed doses and allow for tracking of defaulters. An example is provided in Annex 7.

² WHO, to be published in 2017
Box 13. Immunization registers should include the following data:

- A unique identification number, if possible;
- Registration date (usually the date of the first visit);
- Name of the girl;
- Date of birth;
- Sex of the vaccine recipient (HPV vaccine is only given to girls);
- Name and mobile phone number of parent/guardian, if feasible, to facilitate reminders;
- Space to record date and dose administered (e.g., dose 1 or dose 2);
- Other data of relevance to the immunization programme (including adverse events).

TALLY SHEETS

Tally sheets are the forms that health workers use to document an immunization session by making a record for every dose of vaccine given. Tally sheets should be used at all vaccination sessions whether at the health centre, fixed outreach, school, or conducted by mobile teams. Tally sheets are also useful in tracking both doses delivered and any vaccine doses wasted. An example of a tally sheet for HPV vaccine is provided in Annex 8.

It is recommended that the HPV vaccine tally sheet track the doses given by age (this is particularly important if using a school class or grade as the target population). As this might be new for some national immunization programmes, it is advised that health worker training prior to HPV vaccine introduction carefully review the proper method for using the HPV vaccine tally sheet. Supportive supervision visits should also monitor appropriate use and completion of the tally sheet to improve the quality of data reporting.

IMMUNIZATION CARDS

Immunization or vaccination cards are an essential tool to track immunization history, and are easily adaptable for HPV vaccine. The vaccination card can:

- Enable health workers to determine which doses are due
- Serve as a reminder for the next visit/dose
- Facilitate coverage surveys
- Serve as documented proof of immunization status if required for school entry or for other reasons (i.e. later in life for cervical cancer screening)

While it is always desirable to have an immunization card that includes vaccination over a lifetime, it is recognized that many countries are using vaccination cards only for infant vaccination. In these cases, it will be necessary to create a new vaccination card for adolescent vaccinations that includes HPV. Even if HPV is the only vaccine currently given to this age group, it may be sensible to include options for other vaccines to be added (e.g. Td, dengue). (see Annex 9 for an example HPV vaccination card and Key Resource below for an example of such a card that follows the life course).

For countries using schools as the HPV vaccination location, the vaccination card is often kept at the school until the series is completed, at which time the card is given to the girl for safe-keeping and documentation of completion of both doses of HPV vaccine.
INTRODUCING HPV VACCINE

KEY RESOURCE

Practical guide for the design, use and promotion of home-based records in immunization programmes

This document provides guidance to national immunization programmes on how to improve the design of home based records and how to promote their use among health workers and caregivers.

http://www.who.int/immunization/monitoring_surveillance/routine/homebasedrecords/en/

TRACKING DOSES AND DEFAULTERS

As with other vaccinations, it is important to follow-up eligible girls who fail to present for either the first or second dose of HPV vaccine. High levels of defaulting could be an indication of more systemic problems in the community, such as lack of confidence or trust in the vaccine, or in service delivery, such as stock outs. A system to track drop-outs is an integral part of the Reaching Every District (RED) or Community (REC) strategy. The RED/REC approach can and should be used to ensure high coverage with HPV vaccine (Box 14).

Box 14. Five “RED or REC” components to increase immunization coverage

1. Planning and management of resources – better management of human and financial resources.
2. Reaching target populations – improving access to immunization services by all.
3. Linking services with communities – partnering with communities to promote and deliver services
4. Supportive supervision – regular on-site teaching, feedback and follow-up with health staff.

Two common ways of monitoring and follow-up of defaulters are the immunization registers and reminder cards (sometimes called “Tickler Boxes”).

(i) Using the immunization register – regularly review the immunization register to identify girls who may have failed to receive their second dose of HPV vaccine when due.

(ii) **Reminder cards** – another way to identify “drop-outs or defaulters” is to make copies of the vaccination card for HPV vaccine. File a copy of the card in a box with dividers by month as shown below. The reminder card is put in the month that the missed dose of vaccine is due. Health workers can use community messaging, reminders to parents, mobile phone texts, or other mechanisms to send reminders of the need for attending to receive the missed vaccine dose. Tracking every month will provide consistency and make the exercise a regular part of the work of the health centre staff.

(iii) **Electronic immunization registries (EIRs)** – more and more countries will be developing and implementing computerized registries that include records for each child with personal information as well as vaccination data. EIRs allow automating the generation of listings of children who are due for a vaccine or who have missed a dose, as well as sending recall/reminders by phone, email or letters directly from the EIR to consenting users.

**MONTHLY REPORT**

HPV vaccine immunization data should be collected on a monthly basis at each level of the health system, as is done for all other vaccines on the national immunization schedule. This may be done in a form specifically tracking HPV immunization, or as part of the integrated monthly report. The integrated monthly report contains critical data on most of the components of the immunization system in summary format for both easy recording and easy tracking. It is a valuable tool for management of the programme’s achievements and to monitor progress throughout the year. The integrated monthly report should be adapted when HPV vaccine is added to the national immunization schedule. Annex 10 provides an example of a stand-alone monthly report for HPV vaccination. Additional examples of integrated monthly reports, illustrating the summary nature of the data for all vaccines administered in various formats, can be found in the HPV Vaccine Coverage Monitoring Tool⁴.

If the HPV vaccine delivery strategy only provides vaccination periodically (i.e. every 6 months or annually; not continuously throughout the year) then “zero” reporting will be necessary for the months when HPV vaccine is not given.

**COVERAGE MONITORING**

Calculating HPV vaccine coverage is necessary for monitoring the impact of vaccine on a population, as well as for evaluating the performance of a vaccine programme toward meeting objectives. As with other EPI vaccines, administrative coverage can be supplemented by coverage surveys (see coverage surveys below).

Since HPV vaccination is recommended as a 2-dose series of vaccines administered 6 months apart to 9-14 year-old girls, HPV vaccine coverage monitoring requires collection of coverage data by dose and by 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 coverage monitoring wall chart for HPV vaccination should be maintained and displayed in the health facility. This chart should include the target population of girls at the health facility or catchment area, and record the number of girls vaccinated per month, per dose, over time, until the

target is reached. If campaign-style delivery is used, then setting up the charts showing two time points can be used to provide a visual record of the administrative coverage (per outreach per dose).

**WHO/UNICEF JOINT REPORTING FORM ON IMMUNIZATION**

National immunization programmes provide HPV vaccination to different age groups of young adolescent girls or persons. For international comparison of two-dose HPV vaccine coverage and for calculating regional and global coverage for girls by a certain age, all countries are requested to report the number of HPV doses administered by single year of age after national introduction of HPV vaccine to the international community via the WHO/UNICEF Joint Reporting Form on Immunization (JRF). This form is commonly used for all other routine immunizations and has been adapted to accommodate HPV vaccine (see Table 6).

**Table 6. Excerpt from WHO/UNICEF Joint Reporting Form for HPV vaccine doses administered**

<table>
<thead>
<tr>
<th>HPV VACCINE DOES ADMINISTERED: [YEAR]</th>
<th>FEMALES</th>
<th>A. 1ST DOSE</th>
<th>B. 2D DOSE</th>
<th>C. 3D DOSE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>VACCINE ADMINISTERED (AGE IN YEARS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
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<td>10</td>
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<td>11</td>
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<td>12</td>
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<td>13</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>unknown age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*WHO recommends a 2-dose schedule for girls <15 years of age (Position Paper, Oct 2014). If a 2-dose schedule was used, please leave Column C blank.

Note: 3rd dose reporting only required for years prior to 2015, when the WHO recommended schedule for HPV vaccine was three doses. Some countries are continuing to use a three dose schedule, particularly if they are targeting girls >15 years of age.


**EVALUATION TOOLS**

WHO has adapted the common evaluation tools so that they may be used for HPV vaccination. These tools measure similar outcomes of programme performance as conducted for other new vaccine introductions, but are modified to accommodate several unique features of HPV vaccine delivery.

**POST-INTRODUCTION EVALUATION (PIE)**

Global experience with the introduction of new vaccines is now very extensive, and most countries have introduced at least one or more new vaccines in the last 10 years. For these reasons, WHO no longer recommends that all countries should conduct a post-introduction evaluation (PIE) 6-12 months following national introduction. More simply, the WHO recommendation is now to combine
the assessment of any new vaccine introduction with the next scheduled EPI Programme Review or other evaluation opportunity.

Nevertheless, given the uniqueness of HPV vaccine, some countries may still wish to conduct a PIE or a smaller scale assessment to evaluate the impact of the HPV vaccine introduction on the country’s immunization programme and to rapidly identify problems needing corrective action that are the result of the introduction or that pre-existed.

To assist, WHO has developed a user-friendly PIE tool for assessing the introduction and implementation of HPV vaccination, which includes sample questionnaires and checklists that countries can adapt. Special components deal with involvement of schools and teachers, as well as for more intensive community sensitization and mobilization activities. Copies of the HPV PIE Tool are available from WHO’s Department of Immunization, Vaccines & Biologicals (Contact: vaccines@who.int).

EPI PROGRAMME REVIEWS

EPI programme reviews are undertaken every three to five years and should be adapted to include HPV vaccine once it has been introduced.

WHO has recently revised its methodology for conducting EPI Reviews which recommends integrating immunization-related programme assessments, where feasible, in order to promote efficiency. If an HPV component will be integrated with the EPI Review, the main objectives and critical knowledge gaps regarding HPV introduction should be considered in the Desk Review stage so that these issues can be addressed through specific lines of questioning included in the review tools.

Additional modifications may be required as well, such as interviews with stakeholders or partners concerned specifically with HPV vaccine, and visiting additional sites, such as schools, if applicable.

Copies of the EPI Comprehensive Programme Review methodology are available from WHO’s Department of Immunization, Vaccines & Biologicals (Contact: vaccines@who.int)

VACCINATION COVERAGE SURVEYS

WHO recommends that national coverage surveys include HPV only when at least a full year of HPV vaccine introduction has occurred (to ensure all eligible girls for that year have the opportunity to complete the 2-dose series prior to the conduct of the survey). National coverage surveys are useful to validate administrative data reported throughout the year and allow for comparisons with coverage achieved in other countries.

WHO has recently adapted the vaccination cluster coverage survey manual and it now includes guidance on how to measure HPV vaccine coverage. Even though HPV vaccine delivery strategies may vary, it is recommended that accurate and precise estimates of HPV vaccine coverage be obtained by a certain age, and that if information on coverage by strategy is to be measured, queries about the strategy used to reach the girl and/or oversampling special groups be included. These considerations will help to accommodate sampling issues and hard-to-reach sub-populations (such as out-of-school girls). The working draft of the new WHO Vaccination Cluster Coverage Survey Manual is available at http://www.who.int/immunization/monitoring_surveillance/routine/coverage/en/index2.html
ANNEXES
ANNEX 1. UN POPULATION DIVISION – FEMALE POPULATION BY SINGLE AGE, MAJOR AREA, REGION AND COUNTRY, ANNUAL ESTIMATES 1950-2100

Annual population estimates for single age cohorts for females (and also males) by country are available from the United Nations Population Division website: https://esa.un.org/unpd/wpp/. Single year of age data can be downloaded from tables in Excel format under “Data”, subheading “Interpolated indicators”. The UN Population estimates are revised every two years; the next revision will be in 2017.

1. On the UN Population Division home page, go to “Download Data Files”

2. Under Major topic/Special groupings, select “Interpolated indicators”

3. Select the subgroup in which you are interested (e.g. Age composition: Annual Population by Age - Female)
4. Download Excel file and filter for the year and country you are looking for.

http://esa.un.org/wpp/Excel-Data/EXCEL_FILES/5_Interpolated/WPP2012_INT_F03_3_POPULATION_BY_AGE_ANNUAL_FEMALE.XLS
ANNEX 2. HOW TO PERFORM A SHAKE TEST

HPV vaccine should never be frozen; freezing damages the vaccine. The shake test is used to test a vial that has been suspected of freezing, to see if the vaccine has been damaged by freezing. The below table describes how to perform the shake test.

How to conduct a shake test. This protocol must not be altered. There is only one correct way to conduct a Shake Test.

When to conduct a shake test. The test procedure described below should be conducted on all suspect batches. In the case of international arrivals, the shake test should be conducted on a random sample of vaccine. However, if there is more than one lot in the shipment, the random sample must include a vial taken from each and every lot.

1. Take a vial of vaccine of the same type and batch number as the vaccine you want to test, and made by the same manufacturer.
2. Clearly mark the vial as “FROZEN.”
3. Freeze the vial in a freezer or freezing compartment of a refrigerator until the contents are completely solid.
4. Let it thaw. Do NOT heat it!
5. Take your “TEST” vial from the batch that you suspect has been frozen.
6. Hold the “FROZEN” vial and the “TEST” vial together in one hand.
7. Shake both vials vigorously for 10–15 seconds.
8. Place both vials on a flat surface side-by-side and start continuous observation of the vials until the test is finished.

(NOTE: If the vials have large labels that conceal the vial contents, turn both vials upside down and observe sedimentation in the neck of the vial.)

Use an adequate source of light to compare the sedimentation rates between vials.

9. The TEST vial sediments slower than the FROZEN vial. THEN...
10. Sedimentation is similar in both vials OR The TEST vial sediments faster than the FROZEN vial THEN...

11. Use the vaccine batch. 11. Vaccine damaged: DO NOT USE. Notify your supervisor. Set aside all affected vaccine in a container marked “DAMAGED VACCINE FOR DISPOSAL– DO NOT USE”

12. Discard all affected vaccine once you have received permission to do so.
13. Fill in the Loss/Adjustment Form.

# ANNEX 3. TIMING AND FREQUENCY FOR HPV VACCINE COMMUNICATIONS – A COUNTRY EXAMPLE

<table>
<thead>
<tr>
<th>TIMING</th>
<th>ACTIVITY</th>
<th>FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At least two weeks prior to vaccinations</strong></td>
<td>Billboards/posters placed at the district centre and in each community</td>
<td>Posters can be put up when HPV vaccinations are starting, and should remain until the second dose is complete.</td>
</tr>
<tr>
<td></td>
<td>Messages broadcast on the district radio station</td>
<td>Messages should be broadcast on district radio for two to three weeks prior to each dose.</td>
</tr>
<tr>
<td></td>
<td>Messages broadcast on the community radio station</td>
<td>Messages should be broadcast on the local radio station at least two weeks before vaccination, and two or three times per week for two weeks in each community prior to each dose.</td>
</tr>
<tr>
<td><strong>At least one week prior to vaccinations</strong></td>
<td>Parent meetings held at the school or in the community</td>
<td>One parent meeting should be held in each community at least one week before dose 1.</td>
</tr>
<tr>
<td></td>
<td>Girls’ meetings or information sessions held at the school or in the community</td>
<td>One group discussion or meeting can be held in each school or health facility at least one week before dose 1.</td>
</tr>
<tr>
<td></td>
<td>Messages broadcast on the radio</td>
<td>Messages should be broadcast on the radio twice a day during the week before each dose (local, district, and national radio stations can be utilized).</td>
</tr>
<tr>
<td></td>
<td>Banners and posters placed at the school and health facility</td>
<td>Banners and posters should be put up at identified places in each school or health facility at least one week before each dose.</td>
</tr>
<tr>
<td></td>
<td>Leaflets and information about when vaccination will take place and location of vaccination sites</td>
<td>For each dose, girls and parents should be informed in advance of the date of vaccination and any follow-up vaccination activities that may occur for girls who missed doses.</td>
</tr>
<tr>
<td><strong>Day of vaccinations</strong></td>
<td>Provincial or regional meeting held to launch vaccination</td>
<td>A provincial or regional launch meeting can be held on the day of vaccination, attended by provincial/regional and district staff.</td>
</tr>
<tr>
<td></td>
<td>District meeting held to launch vaccination</td>
<td>A district launch meeting can be held at the district health center, district education department, district authority, or district IEC center, attended by heads of community health centers.</td>
</tr>
<tr>
<td></td>
<td>Current information on vaccination progress broadcast on the community loudspeaker</td>
<td>Updated information should be broadcast twice in each community (on and after vaccination day) at the start of a new HPV vaccination programme.</td>
</tr>
<tr>
<td></td>
<td>Leaflets and information provided at vaccination sites</td>
<td>Girls and parents should be given basic information about the vaccine and HPV, when the next dose should be given and any follow up vaccination activities that may occur for girls who missed doses.</td>
</tr>
</tbody>
</table>
INTRODUCING HPV VACCINE

ANNEX 4. OBSERVED RATE OF VACCINE REACTIONS – HPV VACCINE

The Vaccines

Currently available HPV vaccines are a recombinant viral protein vaccine containing highly purified virus-like particles (VLP) which are the protein shells of the HPV virus (major capsid protein L1) formed by recombinant DNA techniques. The VLP contain no viral DNA. Thus, they cannot infect cells, reproduce or cause disease. The VLP for each virus genotype are purified and then adsorbed onto an adjuvant.

The available vaccines differ in the number of HPV genotypes that they contain, the way that they are manufactured and the adjuvant that they contain. Both Bivalent and Quadrivalent vaccines are highly immunogenic and prevent primary infection with the HPV genotypes and prevent CIN 2/3 adenocarcinoma. Pre-licensure trials indicate a broadly similar safety profile for minor and serious adverse events for each of the vaccines. Post-licensure surveillance data concerning the safety profiles for each vaccine have detected no safety issues to date (as at November 2011) except rare reports of anaphylaxis.

Types of vaccines

<table>
<thead>
<tr>
<th>Vaccine antigens</th>
<th>Excipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quadrivalent</td>
<td>VLP from genotypes 6, 11, 16, 18</td>
</tr>
<tr>
<td>Bivalent</td>
<td>VLP from genotypes 16, 18</td>
</tr>
</tbody>
</table>

Adverse events

Mild adverse events

Local adverse events

Injection site pain is very common, having been reported in up to 80% of vaccinees for Bivalent (EMEA CHMP, 2007) and Quadrivalent vaccine (Markowitz et al., 2007). Severe pains (spontaneous pain or pain that prevented normal activity) was reported for approximately 6% (EMEA CHMP, 2007) of vaccinees. In pre-licensure placebo controlled clinical trials using the Quadrivalent vaccine, injection site reactions consisted of pain (84%) erythema (up to 25%) and swelling (25%), with pain occurring more commonly than in the placebo groups - both for saline only placebo (pain - 49%) and aluminium placebo (pain-75%). Local adverse reactions following Bivalent HPV vaccine were similar with 78% of vaccine recipients experiencing injection site pain compared with 52% who received the adjuvant alone or 59% who received Hepatitis A vaccine. In a trial comparing the two HPV vaccines in over 1,000 women aged 18 to 45, local reactions occurred more frequently with Bivalent than Quadrivalent vaccine. Injection site reactions included pain (92.9% Bivalent, 71.6% Quadrivalent), redness (44.3% Bivalent, 25.6% Quadrivalent) and swelling (36.5% Bivalent, 21.8% Quadrivalent) (Einstein et al, 2009).

Systemic adverse events

In clinical trials prior to licensure of the Quadrivalent vaccine, systemic adverse events were monitored for the first 15 days post vaccination. The only adverse event reported that occurred in greater than 1% of vaccines and occurred more frequently than placebo was pyrexia (10.1 versus 8.4% according to EMEA CHMP (2006), respectively). A number of other systemic adverse events, of minor nature were reported, but these occurred with an occurrence less than a 0.5% difference in the vaccinated group. Mild systemic adverse events possibly related to vaccination included headache, dizziness, myalgia, arthralgia, and gastrointestinal symptoms (nausea, vomiting abdominal pain). In a direct comparison of the Bivalent and Quadrivalent vaccines, systemic reactions were reported at comparable rates, with the exception of fatigue (49.8% (95% CI: 45.5-54.2) vs. 39.8% (35.6-44.1)) and myalgia (27.6% (95% CI: 23.8-31.6) vs. 19.6% (16.3-23.3)), which were reported more frequently amongst recipients of the Bivalent vaccine (Einstein et al., 2009).
Severe adverse events

In pre-licensure trials, no severe adverse events attributable to the vaccine were recorded for either the Quadrivalent or Bivalent vaccine. Post-licensure clinical trials have included a randomized comparative cohort study on the safety of the Quadrivalent and Bivalent vaccines in 18-45 year old women. Systemic adverse events were monitored for 7 days and 30 days post vaccination. No clinically relevant differences were seen between the vaccinated groups (Quadrivalent vs Bivalent) with regard to new onset chronic disease which also included new onset autoimmune disease (Einstein MH et al., 2009). Follow-up of this cohort 18 months after the last dose of HPV vaccine (at 24 months) were similar between groups (Einstein MH et al., 2011).

HPV vaccine and post-marketing surveillance. As of September 15, 2011, approximately 40 million doses of Quadrivalent vaccine were distributed in the U.S. and VAERS received a total of 20,096 reports of adverse events following Quadrivalent vaccination: 19,075 reports among females and 569 reports for males, of which 504 reports were received after the vaccine was licensed for males in October 2009. Of the total number of reports, 92% were considered to be non-serious, and 8% were considered serious (VAERS 2011). Analysis of the currently available reports has not shown an excessive number of serious or unexpected adverse events (Slade et al., 2009). In particular, further investigation of case reports of Guillain-Barré syndrome, blood clots, and deaths have not revealed any pattern suggesting a causal association with vaccination. Analysis of conditions of interest arising among vaccinated and unvaccinated women using the Vaccine Safety Data link was generally reassuring. A non-significant excess of deep vein thrombosis was observed among women who had other risk factors. One vaccine-associated case of anaphylaxis was observed, with an overall rate of one per 1.7 million doses (95% CI 0.04, 9.3) (Gee et al., 2011).

In Australia, over 6 million doses of Quadrivalent vaccine have been used (as of June 2010) with 1534 adverse events reported (Therapeutic Goods Administration, 2008). These reports have included 16 reports of anaphylaxis which met the Brighton case definition for anaphylaxis (Rüggeberg J et al., 2007), and 133 reports of urticarial reactions (or hives). The current estimated rate of anaphylaxis based on doses given in Australia is 2.6 per million. The rate of anaphylaxis following Quadrivalent vaccine based on data from Vaccine Safety Data link in this study was 1.7 cases per million (Gee et al., 2011). The rates for anaphylaxis for other vaccines given to children and adolescents range from 0 to 3.5 per million doses in international studies which have used different case definitions for anaphylaxis (Bohkle et al., 2003).

In the United Kingdom, the Commission on Human Medicines (CHM) considered the MHRA’s safety review of Bivalent vaccine and concluded that no serious new risks have been identified during its extensive use in the UK over 2 years, and that the balance of its benefits and risks remains positive. Similarly reassuring data on Bivalent vaccine was obtained in Italy (Gasparini, 2011), Malaysia (ADRAC Bulletin, 2011), and the Netherlands (van Klooster et al., 2011).

Other safety issues

HPV vaccine in combination with other vaccines. Assessment of concomitant use of the Quadrivalent vaccine and recombinant Hepatitis B vaccine showed no increase in adverse events (Reisinger et al., 2010). Concomitant use of the Bivalent vaccine with combined diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine to girls and young women was generally well tolerated (Garcia-Sicilia et al., 2010).

HPV vaccine in pregnancy. In the absence of well-controlled studies in pregnant women, vaccination with HPV vaccine is not recommended in pregnancy as a precautionary measure. However, some data is available because pregnant women have been enrolled in phase III clinical trials with known pregnancy outcomes and through the establishment of pregnancy registers. In a combined analysis of pregnancy outcomes for women aged up to 45 years, the administration of Quadrivalent human papillomavirus vaccine to women who became pregnant during the phase III clinical trials did not appear to negatively affect pregnancy outcomes (Garland et al., 2009). A pooled analysis of two randomized controlled trials on the risk of miscarriage with Bivalent vaccine provided no evidence overall for an association between HPV vaccination and risk of miscarriage. Of 517 reports of pregnancies enrolled on a register, rates of spontaneous abortions and major birth defects were not greater than those in the unexposed population (Dana et al., 2009). An analysis of phase III trials and post-marketing data identifying reports of 90 pregnancies within 30 days of vaccination showed no increased risk of spontaneous abortion, fetal malformations, or adverse pregnancy outcomes in the general population (Forinash AB et al., 2011)

Syncope in adolescent girls. Post-marketing surveillance has documented a number of cases of syncope in adolescent girls (CDC, 2008). Possibly the rate of syncope is higher when the HPV vaccine is delivered as part of a school programme and vaccine providers should have measures in place to prevent syncope and syncope-related injury from occurring (Bernard DM et al., 2011).
## Summary of mild and severe adverse events - Quadrivalent HPV vaccine

<table>
<thead>
<tr>
<th>Nature of Adverse event</th>
<th>Description</th>
<th>Rate/doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td><strong>Local adverse events</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Injection site reaction</td>
<td>83 per 100</td>
</tr>
<tr>
<td></td>
<td>Erythema and swelling</td>
<td>25 per 100</td>
</tr>
<tr>
<td></td>
<td>Severe - injection site erythema and/or swelling</td>
<td>5.7 per 100</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 inches in size and pain severe</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Systemic adverse events:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>13 per 100</td>
</tr>
<tr>
<td></td>
<td>Urticaria</td>
<td>3 per 100</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>26 per 100</td>
</tr>
<tr>
<td></td>
<td>Myalgia</td>
<td>2 per 100</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>1 per 100</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal disorders</td>
<td>17 per 100</td>
</tr>
<tr>
<td>Severe</td>
<td>Anaphylaxis</td>
<td>1.7 – 2.6 per 10^6</td>
</tr>
</tbody>
</table>

Source: European Public Assessment Report (EMEA CHMP, 2006)

## Summary of mild and severe adverse events - Bivalent HPV vaccine

<table>
<thead>
<tr>
<th>Nature of Adverse event</th>
<th>Description</th>
<th>Rate/doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generally mild</td>
<td><strong>Local adverse events</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Injection site pain</td>
<td>78 per 100</td>
</tr>
<tr>
<td></td>
<td>Swelling</td>
<td>26 per 100</td>
</tr>
<tr>
<td></td>
<td>Redness</td>
<td>30 per 100</td>
</tr>
<tr>
<td></td>
<td><strong>Systemic adverse events:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>33 per 100</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>30 per 100</td>
</tr>
<tr>
<td></td>
<td>Myalgia</td>
<td>28 per 100</td>
</tr>
<tr>
<td></td>
<td>Itching</td>
<td>9 per 100</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>10 per 100</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal symptoms</td>
<td>13 per 100</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
<td>3 per 100</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>1 per 100</td>
</tr>
<tr>
<td></td>
<td>Urticaria</td>
<td>0.46 per 100</td>
</tr>
</tbody>
</table>

Source: Gasparini et al. (2011); European Public Assessment Report, EMEA CHMP (2006)

---

This information sheet has been developed in close collaboration with the Global Advisory Committee on Vaccine Safety (GACVS). GACVS experts are independent and have declared no interests related to the expertise displayed in this product. Information displayed has been developed using primary sources such as Plotkin et al., 2008, Institute of Medicine of the National Academies 2011 and from data derived from a literature search on PubMed in 2008 using key words “vaccine antigen”, “Safety” and “adverse events”. An independent expert provided a first draft which was reviewed by nominated experts and the GACVS. Data of different vaccines that may be found in this product should only be compared if there is indication that a comparative randomized controlled trial has been undertaken. The information sheets will be updated as new information may become available at the following web link: [http://www.who.int/vaccine_safety/vaccrates/en/index.html](http://www.who.int/vaccine_safety/vaccrates/en/index.html)
References


Available online: http://www.who.int/vaccine_safety/initiative/tools/HPV_Vaccine_rates_information_sheet.pdf
### ANNEX 5. SAMPLE AEFI REPORTING FORM

#### REPORTING FORM FOR ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

<table>
<thead>
<tr>
<th><em>Patient name:</em></th>
<th><em>Patient’s full Address:</em></th>
<th><em>Reporter’s Name:</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Institution / Designation, Department &amp; address:</td>
</tr>
<tr>
<td>Telephone:</td>
<td></td>
<td>Telephone &amp; e-mail:</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ M ☐ F</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Date of birth (DD/MM/YYYY):</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ &lt; 1 Year ☐ 1 to 5 Years ☐ &gt; 5 Years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR Age at onset:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Years ☐ Months ☐ Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OR Age Group:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ 0-1 Year ☐ 1 to 5 Years ☐ &gt; 5 Years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health facility (or vaccination centre) name:</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Name of Vaccines Received</em></td>
<td><em>Date of vaccination</em></td>
<td><em>Time of vaccination</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse event(s):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Severe local reaction ☐ &gt;3 days ☐ beyond nearest joint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Seizures ☐ febrile ☐ afebrile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Abcess</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Sepsis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Encephalopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Toxic shock syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Thrombocytopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Anaphylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Fever≥38°C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Other (specify)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date &amp; Time AEFI started (DD/MM/YYYY):</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was the patient hospitalized? ☐ Yes ☐ No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date patient notified event to health system (DD/MM/YYYY):</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Outcome:</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Recovering ☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>☐ Died If died, date of death (DD/MM/YYYY):</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autopsy done: ☐ Yes ☐ No ☐ Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past medical history (including history of similar reaction or other allergies), concomitant medication and other relevant information (e.g. other cases). Use additional sheet if needed:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>First decision making level to complete:</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigation needed: ☐ Yes ☐ No</td>
<td></td>
<td>If yes, date investigation planned (DD/MM/YYYY):</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>National level to complete:</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date report received at national level (DD/MM/YYYY):</td>
<td></td>
<td>AEFI worldwide unique ID:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comments:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*compulsory field

Available online: http://www.who.int/vaccine_safety/publications/en/
EXAMPLE OF GENERIC REPORTING FLOW FOR REPORTING AEFI

1. Community/mother/caretaker
   - Health worker who detects the case
   - District Rapid Response Team
     - Focal person: District Health Officer
   - Regional AEFI Coordinator
     - Focal person: Paediatrician at regional referral hospital
   - National AEFI Task force
     - Focal person: EPI Programme Manager

INTRODUCING HPV VACCINE
ANNEX 6. AID MEMOIRE FOR AEFI INVESTIGATION AND SAMPLE AEFI INVESTIGATION FORM

AEFI Investigation

WORLD HEALTH ORGANIZATION

AIDE MEMOIRE
An adverse event following immunization (AEFI) is a medical incident that takes place after an immunization, causes concern and is believed to be caused by the immunization. Programmes providing immunization services should include a system for AEFI detection and reporting, investigation and management, data analysis, corrective action, relevant communication and evaluation of the system.

The ultimate goal of an investigation is to determine whether the vaccine or immunization process is responsible for the reported event(s) or to find another and correct it if possible, and reassure the public.

There are 4 possible causes of AEFI:

Vaccine reaction: event caused by some component of the vaccine – the active component of the vaccine itself, the preservative, the stabilizer or other. The majority of vaccine reactions are "common" and expected, mild, settle without treatment and have no long-term consequences. More serious reactions are very rare – usually of a predictable (albeit extremely low) frequency;

Programme error: event caused by error in vaccine preparation, handling or administration;

Coincidence: event where something happens after the immunization but is not caused by the vaccine or the programme; and

Injection reaction: event arising from anxiety about the injection (needle).

The purposes of investigating AEFI cases are:

1) to confirm a reported diagnosis of AEFI and clarify the details and outcome;
2) to determine whether unimmunized persons are experiencing the same medical event(s);
3) to investigate the link between the vaccine given and the AEFI;
4) to determine the contribution of operational aspects of the programme to the reported AEFI;
5) to determine whether a reported event was isolated or part of a cluster;
6) to determine the cause of the AEFI so as to provide the best intervention/medical care and take any further action deemed necessary.

In most cases, a preliminary investigation of an AEFI can be made by the health worker who detected the case, e.g. a health centre staff member or a nurse or physician in a hospital.

Serious AEFI cases or AEFI clusters should be investigated immediately with involvement from central levels including epidemiological and/or clinical expertise. A cluster of AEFIs can be defined as two or more cases of the same adverse event related in time, place or vaccine administered.

Inadequate planning or response may lead to a crisis with loss of confidence in the vaccination service. It is essential that programme managers:

1) anticipate the crisis and be prepared to deal with it when it occurs;
2) verify the facts of any event before making any public statement;
3) be familiar with a plan for reacting to any crisis should it happen.
4) be well informed so that appropriate national and regional managers can be rapidly briefed to take charge and deal with political and media enquiries.

☑ Checklist

1. Be prepared
☐ Read the resource documents on reporting, management and investigation of AEFIs.
☐ Develop standards: case definitions for reportable AEFIs, use of reporting forms and investigation procedures.
☐ Designate and train staff to conduct an AEFI investigation using the investigation form.
☐ Train staff on how to collect specimens.
☐ Establish procedure, criteria and designated person for notifying WHO and UNICEF (or UN-supplied vaccine) or other relevant party depending on procurement mechanism.
☐ Establish a National Technical Advisory Committee with representation from major medical organizations.
☐ Identify a spokesperson for public communications.

2. Receiving a report
☐ Ensure immediate reporting of most serious events and rapid attention to reports received.
☐ Verify the information in the report and classify and assess the AEFI using established case definitions. Decide whether it needs further investigating.
☐ If investigation is warranted, travel to the location of the AEFI, or delegate responsibility to another trained person.

3. Investigate and collect data
☐ Ask about the patient.
☐ Ask about the vaccine and other drugs potentially received.
☐ Ask about other vaccines.
☐ Ask about immunization services.
☐ Observe the service in action.
☐ Ask about cases in unvaccinated persons.
☐ Establish a more specific case definition if needed.
☐ Formulate a hypothesis as to what caused the AEFI.

Collect specimens if appropriate:
☐ from the patient.
☐ the vaccine (and diluent if applicable).
☐ the syringes and needles.

4. Dispatch specimens to appropriate testing facility (laboratory, regulatory authority etc.).

5. Analyze the data
☐ Review epidemiological, clinical, and laboratory findings.
☐ Summarize and report findings.

6. Take action
☐ Communicate with health staff.
☐ Communicate findings and action to the parents and public.
☐ Correct problem (based on the cause) by improving training, supervision, and/or distribution of vaccines/injection equipment.
☐ Replace vaccines if indicated.
Key data to be collected

1) **Data on each patient**
   - demographic data about patient, including a unique case number, age, sex, place of residence, family history;
   - history of patient’s present illness - symptoms and when each appeared and its duration, treatment, outcome, diagnosis;
   - history of patient’s past illnesses e.g., reactions to previous vaccine doses, drug allergies;
   - pre-existing disorders, current medications;
   - immunization history - vaccine, number of doses received, date, and place of last immunization or immunizations, mode and site of administration;
   - laboratory results about blood, stool, or other samples, if appropriate and available
   - full autopsy report with toxicological screening and histopathological analysis
   - look for common environmental exposures between patients.

2) **Data about the vaccine(s) (and diluent if applicable) administered to the patient**
   - Lot number(s)
   - Manufacturer(s)
   - Vaccine storage
   - Identify where the vaccine(s) was distributed
   - Whether other children were immunized with same lot or same vial at same session and elsewhere
   - Results of procedures to control vaccine quality
   - Laboratory test results about vaccine, if appropriate.

3) **Programme-related data**
   - Common practices in storing and handling vaccines, and vaccine administration in the health centre in which the suspected immunization (or immunizations) were given. This may help identify products mistakenly used instead of vaccine or diluent

4) **Background data**
   - Establish if cases have been reported from elsewhere and actively look for additional cases among other vaccinees and at large in the community

Role of the district/regional manager

1) **Training**
   Staff should be trained in diagnosing, treating and reporting of AEFIs, and differentiating between mild, non-significant reactions and more serious events.

2) **Supervision**
   Non-serious AEFIs (e.g. abscesses) reported by peripheral health workers should be reviewed with training during site visits.

3) **Investigation and collection of data**
   Following a report of a serious AEFI, the manager should be responsible for investigation, collection and reporting of data. This may be under the overall supervision of a national team.

4) **Communication**
   The manager or designated person should set up the means for continuous communication between health workers and the community, directly and through the media. The public should be informed frequently about what is being done during an investigation and reassured where necessary.

5) **Correction of the problem**
If an AEFI was caused by programme error the actions to be taken will probably include one or more of the following:

- **Logistics**
  Improving logistics will be the appropriate response if programme errors can be traced to the lack of appropriate supplies or equipment, or to a failure in the cold chain.

- **Training**
  Solving operational problems through training will deal with lack of skills and knowledge and with poor attitude.

- **Supervision**
  Regular supervision and intensified when needed e.g., problems detected in reporting or programmatic errors identified.

Did the vaccine or its delivery cause the reactions?

It will be necessary to determine if there is a causal association between the vaccine and the adverse event. In each case the following should be considered:

**Consistency of findings** – are all reported AEFIs the same?

**Temporal sequence** – confirm that the symptoms of AEFI occurred only after, not before, the vaccine was given and if the vaccine-event interval is compatible with a vaccine reaction

**Biological plausibility** – does the medical event seem plausibly due to an effect of the vaccine or other concomitant or preceding conditions?

**Previously known reaction** – check if this type of reaction is known to be related to the vaccine and with which frequency

**Specificity and strength of association** – establish if the same events are being reported in unvaccinated persons and if so, how often and if the cluster is limited to one health center or not

**Concomitant or preceding conditions**

AEFI evaluation requires a 2 by 2 table of exposures and outcomes and data should be collected in order to more fully complete the table and calculate a risk of event from receipt of the vaccine i.e. (a+c)/(b+d). Cell a represents case reports only.

### AEFI evaluation

<table>
<thead>
<tr>
<th>Vaccinated</th>
<th>Adverse Event</th>
<th>No Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a</td>
<td>c</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>b</td>
<td>d</td>
</tr>
</tbody>
</table>

**Suggested steps for the identification of the most likely cause of a cluster of AEFIs**

**Words of advice**

- The investigation should start within 24 hours of notification
- There is seldom need to test the vaccine unless clearly indicated by the epidemiologic investigation, but cold chain should be maintained
- A national committee can be very helpful in reviewing the outcome of the investigation and communication of findings
- Access medical files
- Rule out alternative aetiologies than the vaccination. The fact that previously known reaction are being reported in unvaccinated persons and if so, how often and if the cluster is limited to one health center or not
- Have direct discussions with the patients or parents if possible

Additional information on the definitions, monitoring, management and investigation of AEFIs can be found on the World-Wide Web at [www.who.int/immunization_safety/en](http://www.who.int/immunization_safety/en)

Vaccine Assessment and Monitoring
Department of Immunization, Vaccines, and Biologicals
World Health Organization
20 avenue Appia, 1211 Geneva 27, Switzerland
Tel: +41 22 791 4468 Fax: +41 22 791 4210
Email: immunizationsafety@who.int

Available online: [www.who.int/vaccine_safety/initiative/investigation/AEFI_Investigation_Aide_Memoire.pdf](http://www.who.int/vaccine_safety/initiative/investigation/AEFI_Investigation_Aide_Memoire.pdf)
## AEFI INVESTIGATION FORM

(Only for Serious Adverse Events Following Immunization – Death / Disability / Hospitalization / Cluster)

### Section A
#### Basic details

<table>
<thead>
<tr>
<th>Province/State</th>
<th>District</th>
<th>Case ID</th>
</tr>
</thead>
</table>

Place of vaccination (✓): ☐ Govt. health facility ☐ Private health facility ☐ Other (specify) ___________

Vaccination in (✓): ☐ Campaign ☐ Routine ☐ Other (specify) ___________

Address of vaccination site:

Name of Reporting Officer: ____________________________

Date of investigation: __ __ / __ __ / __ __ __ __

Date of filling this form: __ __ / __ __ / __ __ __ __

Designation / Position: ____________________________

This report is: ☐ First ☐ Interim ☐ Final

Telephone # landline (with code): ____________________________

Mobile: ____________________________

E-mail: ____________________________

<table>
<thead>
<tr>
<th>Patient Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>(use a separate form for each case in a cluster)</td>
</tr>
</tbody>
</table>

Sex: ☐ M ☐ F

Date of birth (DD/MM/YYYY): __ __ / __ __ / __ __ __ __

OR Age at onset: __ __ years __ __ months __ __ days

OR Age group: ☐ < 1 year ☐ 1-5 years ☐ > 5 years

Patient’s full address with landmarks (Street name, house number, locality, phone number etc.): ____________________________

### Section B
#### Relevant patient information prior to immunization

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Finding</th>
<th>Remarks (if yes provide details)</th>
</tr>
</thead>
</table>

Past history of similar event Yes / No / Unkn

Adverse event after previous vaccination(s) Yes / No / Unkn

History of allergy to vaccine, drug or food Yes / No / Unkn

Pre-existing illness (30 days) / congenital disorder Yes / No / Unkn

History of hospitalization in last 30 days, with cause Yes / No / Unkn

Patient currently on concomitant medication? (If yes, name the drug, indication, doses & treatment dates) Yes / No / Unkn

Family history of any disease (relevant to AEFI) or allergy Yes / No / Unkn

For adult women

- Currently pregnant? Yes (weeks) __ __ / __ __ / __ __ __ __ / No / Unknown

- Currently breastfeeding? Yes / No __ __ / __ __ __ __

For infants

- The birth was ☐ full-term ☐ pre-term ☐ post-term. Birth weight: __ __ / __ __ / __ __ __ __

- Delivery procedure was ☐ Normal ☐ Caesarean ☐ Assisted (forceps, vacuum etc.) ☐ with complication (specify)
### Section C Details of first examination** of serious AEFI case

<table>
<thead>
<tr>
<th>Source of information (all that apply):</th>
<th>Examination by the investigator</th>
<th>Documents</th>
<th>Verbal autopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **If from verbal autopsy, please mention source:**

**Name of the person who first examined/treated the patient:**

**Name of other persons treating the patient:**

**Other sources who provided information (specify):**

**Signs and symptoms in chronological order from the time of vaccination:**

**Name and contact information of person completing these clinical details:**

<table>
<thead>
<tr>
<th>Designation:</th>
<th>Date/time</th>
</tr>
</thead>
</table>

**Instructions** – Attach copies of ALL available documents (including case sheet, discharge summary, case notes, laboratory reports and autopsy reports) and then complete additional information NOT AVAILABLE in existing documents, i.e.

- **If patient has received medical care** – attach copies of all available documents (including case sheet, discharge summary, laboratory reports and autopsy reports, if available) and write only the information that is not available in the attached documents below.

- **If patient has not received medical care** – obtain history, examine the patient and write down your findings below (add additional sheets if necessary).

**Provisional / Final diagnosis:**

## ANNEX 7. SAMPLE HPV VACCINE REGISTER (INTEGRATED WITH OTHER VACCINES)

Region: ___________________ District: _______________ Health Facility: ____________________________

<table>
<thead>
<tr>
<th>No.</th>
<th>IDENTIFICATION</th>
<th>RESIDENCE</th>
<th>HPV VACCINATION</th>
<th>Td VACCINATION</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ID</td>
<td>Name</td>
<td>Date of Birth</td>
<td>Sex M/F</td>
<td>Prov.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>District</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Address</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Telephone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Females 9 - 14 years</th>
<th>Adolescents 9 - 14 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose 1 (DATE)</td>
<td>Dose 2 (DATE)</td>
</tr>
<tr>
<td></td>
<td>Dose 1 (DATE)</td>
<td>Dose 2 (DATE)</td>
</tr>
<tr>
<td></td>
<td>Dose 3 (DATE)</td>
<td>Dose 3 (DATE)</td>
</tr>
</tbody>
</table>

*Please refer to WHO position paper on Tetanus vaccines for recommended schedules: http://www.who.int/immunization/wer8120tetanus_May06_position_paper.pdf
ANNEX 8. SAMPLE TALLY SHEET

Sample tally sheet to record number of HPV doses given on single vaccination day

Date: ___/___/___  Region: _____________  District: ______________  Health Facility: _____________

Service Delivery Strategy (circle one): fixed/outreach/school. Location: _____________________

If school, grade: ____________  Total number of eligible girls in the class: ______________

<table>
<thead>
<tr>
<th>Girls</th>
<th>HPV first dose (HPV1)</th>
<th>Total</th>
<th>HPV second dose (HPV2)</th>
<th>Total</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 or more years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## ANNEX 9. SAMPLE VACCINATION CARD

Sample vaccination card from South Africa, which includes parental consent and background information on the HPV vaccine.

### Why HPV Vaccine?
- **Cervical cancer**
  - HPV is a viral infection that can cause cervical cancer
- **HPV vaccine**
  - Reduces your chances of developing cervical cancer

### Who gets the HPV vaccine?
- Given to all girls in Grade 4 that are over 9 years

### Who should not get vaccinated?
- Girls under 9 years
- Girls who had a severe illness recently or are very ill now

### How is it given?
- Injection in 2 doses
  - Second dose given 6 months after first dose

### Table: Sample Vaccination Card

<table>
<thead>
<tr>
<th>Why HPV Vaccine?</th>
<th>Y/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical cancer</td>
<td></td>
</tr>
<tr>
<td>HPV vaccine</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Who gets the HPV vaccine?</th>
<th>Y/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Given to all girls in Grade 4 that are over 9 years</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Who should not get vaccinated?</th>
<th>Y/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls under 9 years</td>
<td></td>
</tr>
<tr>
<td>Girls who had a severe illness recently or are very ill now</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How is it given?</th>
<th>Y/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection in 2 doses</td>
<td></td>
</tr>
<tr>
<td>Second dose given 6 months after first dose</td>
<td></td>
</tr>
</tbody>
</table>

### Sample Vaccination Card

<table>
<thead>
<tr>
<th>Parent please complete and return to school</th>
<th>Parent please complete</th>
<th>Y/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID. No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surname:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of birth:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name of School:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade:</td>
<td>Date:</td>
<td></td>
</tr>
<tr>
<td>Name of parent/guardian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hereby grant permission for my daughter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Name of daughter) to receive the HPV vaccination.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Signature | Date: | |
|-----------|-------| |

<table>
<thead>
<tr>
<th>For official use only</th>
<th>Signature of Vaccinator</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch no.</td>
<td>Dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HPV 1</td>
<td>HPV 2</td>
</tr>
</tbody>
</table>

| For official use only | Date of Next Vaccine | |
|-----------------------|----------------------| |
|                        | HPV 2 | |
## ANNEX 10. SAMPLE MONTHLY VACCINATION REPORT

Monthly Report – Human Papillomavirus Vaccine

Date: ___/___/___ Region: _____________ District: _______________

<table>
<thead>
<tr>
<th>Age/Strategy</th>
<th>Target Pop.</th>
<th>HPV first dose (HPV1)</th>
<th>HPV second dose (HPV2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Fixed</td>
<td>Outreach</td>
</tr>
<tr>
<td>9 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 or more years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ANNEX 11. FREQUENTLY ASKED QUESTIONS (FAQS)

Why are HPV vaccines needed?
Certain human papillomavirus (HPV) types cause cancer, including: cervical, vulvar, vaginal, penile, and anal 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 an important tool for 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 4th most common cancer in women in the world. Of the 266,000 women who die every year from cervical cancer, over 85% live in developing countries.

What WHO prequalified HPV vaccines are currently available?
Two HPV vaccines are currently prequalified by WHO. As of 2016, HPV vaccine has been introduced into the national immunization program in more than 65 countries. These vaccines are Cervarix® (GlaxoSmithKline) and GARDASIL® or Silgard® (Merck & Co.).

In 2016, a third vaccine (9-valent, GARDASIL 9®) is being reviewed for WHO prequalification.

How are the currently available HPV vaccines similar?
All 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.

All vaccines have been shown to prevent cervical pre-cancers in women.

All vaccines are very safe.

All vaccines are non-infectious and cannot cause disease.

All vaccines are given as injections and require two doses.

How are the HPV vaccines different?
The vaccines have different adjuvants—a substance that is added to the vaccine to increase the body’s immune response.

Two of the vaccines (the quadrivalent and the 9-valent) protect against HPV types 6 and 11, the types that cause most genital warts in females and males.

Who should get HPV vaccine?
The WHO recommended target population for HPV vaccination is girls who are 9-14 years old. The vaccines are not licenced for use in girls younger than 9 years of age.

Why is HPV vaccine recommended at ages 9-14 years old?
For the HPV vaccine to work best, it is very important for preteens to get two doses 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 two HPV doses (shots)?

Two doses (shots) are recommended 6-12 months apart.

What is the maximum interval between HPV doses? If a child received only one dose, and presents again 2 years later, should the series be continued?

There is no maximum interval between HPV vaccine doses, hence no need to restart the series. The child should be vaccinated and the vaccination recorded as the 2nd dose.

What is the minimum interval between doses?

HPV vaccine doses should be given at least 5 months apart. If the interval between doses is shorter than 5 months, then a third dose should be given at least 6 months after the first dose.

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 injection 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 diseases (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. Receiving 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 received 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. Girls 9-14 year old who are HIV positive, should however receive an additional dose (3 doses total) to be fully protected.

Can females with physical disabilities be vaccinated?

Yes. Physical handicap is not a contraindication for HPV vaccination.
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 9-14 year old girls is more cost-effective in reducing cervical cancer than including boys.

What should be done if boys are given the HPV vaccine in error?
There is no harm for boys to receive HPV vaccine. If boys are accidently given HPV vaccine this is a programmatic error and training/supervision should be undertaken to correct. For ethical reasons and to prevent the spread of rumours, the “mistake” should be explained to the boys and their parents/guardians (emphasizing that it is safe and in countries elsewhere e.g. Austria, Australia, and United States, boys are vaccinated with HPV). If the vaccine used was the quadrivalent or 9-valent (which protect against genital warts) then the 2nd dose should be offered to the boys. As the bivalent vaccine is not licensed for use in boys, a 2nd dose should not be offered.

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.
This document is intended for use by national immunization programme managers and immunization partners to inform the policy discussions and operational aspects for the introduction of HPV vaccine into national immunization programmes and to provide up-to-date references on the global policy, as well as the technical and strategic issues related to the introduction of HPV vaccine.