Human papillomavirus (HPV) vaccines

Summary of WHO Position Paper

WHO position paper on Human papillomavirus (HPV) vaccines
Weekly Epidemiological Record 16 December 2022

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Executive summary

1. Infection with HPV can become persistent and cause pre-cancerous lesions that may progress to cervical cancer
   A. HPV infections, the majority of which are cleared by natural immunity, **take several decades to progress to pre-cancer and invasive cancers.**
   B. Progression to invasive cancer is more rapid in immunocompromised individuals and they are at six-times increased risks of cervical cancer.
   C. **Annual disease burden for cervical cancer, the most important cancer caused by HPV infection** is estimated at 570 000 cases and 340 000 deaths (Globocan, 2022)

2. **Available HPV vaccines are safe and highly effective, provide long-term protection** against HPV infection and HPV related cancers. All HPV vaccines can be used to eliminate cervical cancer. Vaccination with HPV does not eliminate the need for screening later in life, since the existing vaccines do not protect against all high-risk HPV types.

3. WHO recommends inclusion of HPV in immunization programmes and to reach as a priority adolescent girls between the ages of 9 and 14 year. The following schedules can be used:
   A. **Single or two doses of HPV vaccine** administered to adolescents from 9 to 20 years of age
   B. **Two doses of HPV vaccine** administered to those >20 years of age.
Background of HPV infection

- **Human papillomavirus (HPV)** is the most common viral infection of the reproductive tract, causing a range of conditions in men and women, including **cervical cancer**.

- **While more than 200 types** are identified, 12 HPV types are defined as high-risk and cause cancer.

- While most HPV infections are **asymptomatic and resolve spontaneously**, persistent infection can result in disease.

- Progression to invasive cancer is more rapid in **immunocompromised individuals** and they are at **six-times increased risks** of cervical cancer.

- Annual disease burden for cervical cancer is estimated at **570,000 cases** and **340,000 deaths** (in 2022)

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**Key take-aways**

HPV is a common **sexual transmitted** virus.

**Persistent infection** can lead to HPV-related cancer, including **cervical cancer**.
**Epidemiology of HPV types and cervical cancer**

**Key take-aways**

HPV type 16 and 18 account for more than 70% of cervical cancer globally and all licensed vaccines provide direct protection against these types.

*These percentages represent the global prevalence of HPV types attributed to cervical cancer, which varies across different regions.*
HPV-related Disease

Disease overview

• HPV spreads through contact with infected genital skin, mucous membranes, or bodily fluids, including through sexual intercourse and oral sex.
• Most HPV infections (70-90%) are asymptomatic and resolve within 1-2 years; persistent infection can lead to precancerous lesions and invasive carcinoma.

Cervical cancer

• About 5–10% of infected women develop persistent infection, progressing to precancerous lesions (CIN) and potentially cancer.
• The progression from HPV infection to invasive carcinoma usually takes 15–20 years.
• Women living with HIV (WLWH) have a six-fold higher risk of developing cervical cancer.

Other cancers and diseases

• HPV is linked to squamous cell carcinomas of the anus, vulva, vagina, penis, oropharynx, oral cavity, and larynx.
• Low-risk HPV types can cause anogenital warts, which can be difficult to treat and rarely become malignant.
• HPV can cause recurrent respiratory papillomatosis (RRP), with warts forming in the respiratory tract, leading to significant morbidity and potential malignancy.

Key take-aways

Most HPV infections are asymptomatic and clear within 1-2 years whereas persistent infection can lead to invasive cancer.
Immune response, diagnosis, and treatment

Immune response after HPV infection
- HPV infections do not induce a strong immune response; seroconversion takes about 8-12 months.
- 70–80% of women seroconvert after natural infection, but with low antibody levels; fewer men seroconvert.
- Immunity to natural HPV infection does not consistently protect against reinfection.

Diagnosis of cervical HPV infection/Disease
- HPV infection detected through HPV testing (DNA or mRNA) on cervical or vaginal samples.
- Cervical cytology (Pap test) and visual inspection with acetic acid identify precancerous lesions and early cancer.
- WHO recommends validated HPV DNA testing in a screen-and-treat approach starting at age 30 (or 25 for immunocompromised women), repeated every 5–10 years (3-5 years for immunocompromised women).

Treatment of cervical disease
- No virus-specific treatment for HPV, but screening and treating cervical precancerous lesions prevent cervical cancer.
- Treatments include ablative methods (thermal ablation, cryotherapy) and excisional treatments (LLETZ, CKC) for non-ablative candidates.

Key take-aways
WHO recommends validated HPV DNA testing starting at age 30, repeated every 5-10 years for diagnosis of cervical HPV infection.
Six prophylactic HPV vaccines are currently licensed:
 - Bivalent vaccines: Cervarix, Cecolin, Walrinvax
 - Quadrivalent vaccines: Gardasil, Cervavax
 - Nonavalent vaccines: Gardasil-9

Five prophylactic HPV vaccines are prequalified by WHO (As of August 2024); Cervarix, Cecolin, Walrinvax, Gardasil, and Gardasil-9

All HPV vaccines protect against high-risk HPV types 16 and 18. The nonavalent vaccine are also effective against HPV types 31, 33, 45, 52, and 58. The quadrivalent and nonavalent vaccines also protect against HPV types 6 and 11, which cause anogenital warts.

Some bivalent and quadrivalent vaccines provide cross protection against these HPV types not included in the vaccine

HPV vaccines are administered intramuscularly

The on-label vaccination schedule depends on the age of recipient: two doses for ages 9–14 years and three doses for the ages 15 and older
• **HPV vaccines have shown high efficacy** against HPV infection and in preventing high-grade cervical, vulvar, and vaginal lesions, especially when administered **before HPV exposure**.

• HPV vaccine programme have led to **substantial reductions in HPV prevalence** and related diseases, with **herd immunity benefits** observed in unvaccinated population.

• Recent studies have shown that a **single dose of HPV vaccine offer similar protection** as multidose regimens. Clinical trials and observational studies report **high seropositivity and significant protection** against HPV infection with single dose.

• HPV vaccines provide **long lasting protection** with multidose schedules. Antibody titres remain high for **at least 12 years**.

• **HPV vaccines are safe.** Local reactions (e.g., pain at the injection site) and mild systemic reactions (e.g., headache) are common. Severe adverse events are extremely rare.
WHO Position along 4 dimensions

A Vaccine strategy
B Target groups & Schedule
C Special considerations & safety
D Monitoring & Research
Summary of WHO Position

- HPV vaccines should be introduced as part of a comprehensive strategy to prevent cervical cancer and other diseases caused by HPV. HPV vaccination is a primary prevention and does not eliminate the need for screening later in life.

Primary and secondary target groups

- WHO recommends primary target for HPV vaccination is girls aged 9-14 years old.
- Immunocompromised individuals and those who have faced sexual abuse should be targeted as a priority.
- Vaccination of secondary target populations, including female aged ≥ 15 years, boys, older males or MSM, is recommended only if this is feasible and affordable.

Vaccination Schedule

- Two-dose schedule can be used in the primary target group from 9 years of age and for all older age groups. The minimum interval between first and second dose is 6 months.
- As an alternative option, single-dose schedule can be used in girls and boys aged 9–20 years.
- Individuals known to be immunocompromised should receive at least two doses (minimum 6 months interval) and, where possible, three doses.
WHO Position- Vaccination strategies

Delivery strategies
- HPV vaccination can be introduced through a combination of delivery strategies; schools, health facilities, community outreach or campaigns.
- Countries should choose sustainable strategies compatible with:
  - Existing delivery infrastructure and cold chain capacity
  - Financial resources and affordability
  - Maximizing possible coverage
- Phased introductions should be a temporary measure for large populations or when resources are limited.

Primary objective
- Aim to achieve the highest possible population protection for girls by age 15
- Provide multiple opportunities for girls to receive HPV vaccines.

Catch-up Vaccination
- Implement catch-up vaccination for girls aged 9 to 18 years old during the HPV vaccine introduction. This results in faster and greater population impact due to herd protection. It is cost-effective and allows for economies of scale in delivery.

Key take-aways
Combination of delivery strategies, including school delivery is important for successful HPV introduction.
Implement catch-up vaccination for 9-18 years old for HPV vaccine introduction.
WHO Position- Target group and immunization schedule

Primary and secondary target groups
• WHO recommends primary target for HPV vaccination is girls aged 9-14 years old.
• Priority target groups also include immunocompromised individuals and those who have faced sexual abuse.
• Vaccination of secondary target populations, including female aged ≥ 15 years, boys, older males or MSM, is recommended only if this is feasible and affordable.

Vaccination schedule
• Two-dose schedule can be used in the primary target group from 9 years of age and for all older age groups. The minimum interval between first and second dose is 6 months. A 12-month schedule results in higher GMTs and is suggested for programmatic and efficacy reasons.
• As an alternative option, single-dose schedule can be used in girls and boys aged 9–20 years.
• Individuals known to be immunocompromised should receive at least two doses (minimum 6 months interval) and, where possible, three doses.

Choice of HPV vaccine
• All licensed HPV vaccines offer comparable immunogenicity, efficacy, and effectiveness for the prevention of cervical cancer.
• For use in single-dose schedules, HPV vaccines products with 1-dose efficacy data or with immunobridging are recommended.

Key take-aways
Primary target cohort is girls aged 9-14 years old.
HPV vaccine can be given in single- or two-dose schedules for 9-20 years of age.
WHO Position: Special consideration and safety

Vaccination of special populations

- Immunocompromised individuals and those who have faced sexual abuse are at higher risk for HPV-related diseases and should be prioritized for HPV vaccination.

Co-administration with other vaccines

- HPV vaccines can be co-administered with other vaccines (both live and non-live) using separate syringes and injection sites.
- Co-administration with tetanus-diphtheria (Td) booster doses should be considered to improve efficiency of delivery.

Interchangeable use of HPV vaccines

- Efforts should be made to administer the same vaccine for all doses. However, any available HPV vaccine can be used if the prior vaccines is unknown or unavailable.

Safety

- HPV vaccines are safe. Adverse events are generally mild and short-lived.
- Safety data in pregnancy are reassuring but limited; HPV vaccination is not recommended during pregnancy. Termination of pregnancy is not necessary if vaccinated inadvertently.
- Breastfeeding is not a contraindication.
- To prevent syncope, observe vaccinees seated for 15 minutes post vaccination.

Key take-aways

HPV vaccines can be co-administered with other vaccines.

HPV vaccines have shown excellent safety profile.
WHO Position- Monitoring and research priorities

Monitoring

- HPV vaccine coverage should be tracked through national immunization data reporting systems, registries, and periodic surveys.
- Vaccine effectiveness monitoring requires substantial resources and may not be suitable for all countries.
- All countries should consider developing population-based cancer registries and improve the integration of immunization, screening services, and cancer registries.
- Surveillance should be in place to monitor HPV vaccine safety, including prompt investigation of any serious adverse events.

Research priorities

- Generate evidence on the long-term immunogenicity, efficacy and duration of protection of single-dose schedule among girls aged 9-14 years; boys; older women and men; and children under 9 years.
- Prioritize evidence on the immune response and efficacy of reduced dose schedules in immunocompromised individuals, especially those who received a single-dose HPV vaccine prior to HIV seroconversion.
- Conduct implementation research to identify strategies to improve and sustain HPV vaccine uptake, focusing on high-risk populations and considering integration of life-course vaccination, primary health care, and cervical cancer screening.

Key take-aways

Consider developing population-based cancer registries.

Generate evidence on single-dose schedule for populations, especially for immunocompromised individuals.
Summary of WHO Position Paper on HPV vaccines – December 2022

In case of additional questions, please reach out to the SAGE Secretariat at sageexecsec@who.int