



Considerations for Human Papillomavirus (HPV) Vaccine Product Choice

second edition



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Considerations for human papillomavirus (HPV) vaccine product choice, second edition

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Background

This is an updated, second edition of the document Considerations for Human Papillomavirus (HPV) Vaccine Product Choice (1). It incorporates changes to reflect WHO prequalification of a new bivalent product (Walrinvax®) in August 2024 and the review of evidence on the one-dose use of Cecolin® by WHO's SAGE Steering Group on Vaccination Policy Guidance on 23 August 2024.

This document summarizes current technical and programmatic information on WHO-prequalified human papillomavirus (HPV) vaccine products in order to facilitate informed country choices for HPV vaccine introduction (or product switch within immunization programmes). Since 2009, five HPV vaccine products have been prequalified by WHO. They include three bivalent products (Cecolin®, manufactured by Xiamen Innovax Co. Ltd., Cervarix™, manufactured by GlaxoSmithKline Biologicals, and Walrinvax®, manufactured by Yuxi Zerum Biotechnology Co., Ltd.), one quadrivalent product (Gardasil®, manufactured by Merck Vaccines), and one nonavalent product (Gardasil-9®, manufactured by Merck Vaccines). One quadrivalent product (Cervavac®) is nationally licensed.

The primary objective of this document is to provide comprehensive information on HPV vaccine products, including scientific evidence, vaccine pricing, presentations, cold chain and storage requirements and more. This information enables countries to compare different HPV vaccine products and make informed decisions regarding the inclusion of HPV vaccine in their national immunization programmes.

Development

A review was conducted with reference to the latest [WHO position paper on HPV vaccines](#) (2) which was published in December 2022 and already contains a compilation of scientific evidence on HPV vaccine efficacy, effectiveness and safety. The methods followed by SAGE and the processes for preparation of vaccine position papers are described at: <https://www.who.int/publications/m/item/who-position-paper-process>. A thorough manual search was also conducted to identify recently generated evidence, and the original publications cited in the WHO position paper were revisited to verify the scientific evidence. Additionally, product information was collected from publicly available sources.

The final draft was subjected to peer review which involved rigorous scrutiny of scientific evidence and alignment with the requirements of countries. While it represents an expert summary, this paper is not a formal WHO recommendation or guideline. Those contributing to the development of this document have completed the WHO Declaration of Interests for WHO Experts and have been found to have no conflicts of interest in the area of HPV vaccines.

WHO position on HPV vaccines

The 2022 WHO position paper presents the current policy recommendations for HPV vaccines in prevention of HPV-related disease in children aged 9 years or older, with the priority purpose of preventing cervical cancer. Cervical cancer accounts for 82% of all HPV-related cancers in 2018 (3). The 2020 WHO global strategy to accelerate the elimination of cervical cancer as a public health problem recommends that HPV vaccines should be included in all national immunization programmes and should reach 90% of girls of 15 years of age by 2030 (4). The HPV position paper does not express a preference between prequalified HPV products and states the following:

- All currently licensed bivalent, quadrivalent and nonavalent HPV vaccines have excellent safety profiles and offer comparable immunogenicity, efficacy and effectiveness for the prevention of cervical precancer and cancer, which are mainly caused by HPV types 16 and 18.
- Most HPV vaccines are licensed for use in females and males. Currently, Cecolin® and Walrinvax® are only licensed for use in females.
- The choice of HPV vaccine should be based on an assessment of locally-relevant data and on a number of considerations, including the scale of the HPV-associated public-health problem (cervical cancer, other HPV-associated cancers, anogenital warts), the population for which the vaccine has been approved, product characteristics (including single-dose efficacy if the single-dose schedule option is being considered), price and programme considerations.

Vaccine characteristics

- All HPV vaccines are produced by using recombinant DNA and cell-culture technology. They do not contain live biological products or viral DNA and are therefore non-infectious. HPV vaccines are prepared from the L1 structural protein of HPV in the form of virus-like particles (VLPs)¹, using different expression systems (producer cells). HPV vaccine products contain different adjuvants and do not contain preservatives or antibiotics. They are administered by intramuscular injection.
- When considering the composition of the four prequalified HPV vaccine products, there is a key difference in the number and selection of VLPs/HPV types included in the products. The qualitative differences in composition of the currently prequalified HPV vaccines are included in Table 1, and those of HPV vaccines currently under review for WHO prequalification are shown in Table 2.

¹ HPV type-specific empty shells named virus-like particles (VLPs) self-assemble spontaneously from pentamers of the L1 major capsid protein.

Table 1. Characteristics and qualitative composition of prequalified HPV vaccines (5)

Vaccine	Bivalent			Quadrivalent	Nonavalent
Trade name	Cecolin®	Cervarix™	Walrinvax®	Gardasil®	Gardasil-9®
Manufacturer	Xiamen Innovax Biotech Co. Ltd.	GlaxoSmithKline Biologicals SA	Walvax Biotechnology Co. Ltd.	Merck Vaccines	Merck Vaccines
Date of WHO prequalification	14 October 2021	08 July 2009	02 August 2024	20 May 2009	09 February 2018
Antigens (VLP types)	HPV 16 HPV 18	HPV 16 HPV 18	HPV 16 HPV 18	HPV 16 HPV 18 HPV 6* HPV 11*	HPV 16, HPV 18, HPV 31, HPV 33, HPV 45, HPV 52, HPV 58, HPV 6*, HPV 11*
Adjuvant	Aluminium hydroxide	AS04 (Aluminium hydroxide and 3-deacylated monophosphoryl lipid A)	Aluminium phosphate	Aluminium hydroxy-phosphate Sulfate	Aluminium hydroxy-phosphate Sulfate
Expression system/ producer cells	<i>Escherichia coli</i>	Baculovirus derived from <i>Trichoplusia ni</i>	<i>Pichia pastoris</i>	<i>Saccharomyces cerevisiae</i> (baker's yeast)	<i>Saccharomyces cerevisiae</i> (baker's yeast)

*HPV types considered non-oncogenic cause approximately 90% of genital warts (6).

Table 2. Characteristics and qualitative composition of HPV vaccines currently nationally licensed (not WHO-prequalified)

Vaccine	Quadrivalent
Trade name	Cervavac®
Manufacturer	Serum Institute of India Pvt. Ltd. (SII)
WHO prequalification status	Not submitted
Antigens (VLP types)	HPV 16 HPV 6* HPV 18 HPV 11*
Adjuvant	Aluminium hydroxide
Expression system/ producer cells	<i>Hansenula</i>

Vaccine safety

- The safety of HPV vaccines has been reviewed as part of the WHO prequalification process and by the Global Advisory Committee on Vaccine Safety (GACVS). No safety concerns have been identified (7).
- Post-marketing surveillance has detected no serious safety issues to date except rare hypersensitivity reports including anaphylaxis. Data from all sources continue to be reassuring regarding the safety profile of HPV vaccines currently in global use. A summary of local and systemic reactions following vaccination is included in Table 3.
- A systematic review of studies on the safety of HPV vaccines found little-to-no difference among recipients of bivalent, quadrivalent and nonavalent HPV vaccines with regard to serious adverse events or new-onset chronic disease, including new-onset autoimmune disease (8).
- A well-conducted population-based study on post-marketing safety surveillance showed no association between HPV vaccine and new-onset chronic conditions, including autoimmune disease, after vaccination (9). Data are reassuring that HPV vaccine does not increase risk of Guillain-Barré syndrome, Bell's palsy, complex regional pain syndrome (CRPS), or postural orthostatic tachycardia syndrome (POTS). No association was found between HPV vaccination and infertility.

Table 3. Local and systemic adverse events following HPV vaccination

Vaccine	Bivalent		Quadrivalent	Nonavalent
Trade name	Cecolin®	Cervarix™	Gardasil®	Gardasil-9®
Local reactions (8)	Overall reported: Injection site pain (35–88%), redness (5–40%), swelling (4–35%), severe pain* (6%)			
	May result in more local reactions than quadrivalent			Slightly more likely to report pain and swelling than quadrivalent
Systemic reactions (9)	Overall reported events generally mild and self-limiting: headache, dizziness, myalgia, arthralgia, gastrointestinal symptoms (nausea, vomiting, abdominal pain)			
	49%	69%	55%	
	Rare: hypersensitivity reactions including anaphylaxis			
Special considerations	Post-vaccination syncope and immunization stress-related responses have been observed but can be minimized with appropriate preparation (10). To avoid injury from fainting, vaccine recipients should be seated and observed for at least 15 minutes after administration of HPV vaccine.			

*Spontaneous pain or pain preventing normal activities.

Contraindications, precautions and use in pregnancy

- Contraindications: known history of severe allergic reaction to any component of HPV vaccine, or severe allergic reaction after the first dose of HPV vaccine.
- Precautions: to prevent syncope and/or injury from fainting, vaccine recipients should be seated and observed for at least 15 minutes following administration of HPV vaccine.
- In the absence of well-controlled studies in pregnant women, vaccination of pregnant women is not recommended. Pregnancy testing is not necessary before vaccination.
- Inadvertent vaccination during pregnancy is not an indication for pregnancy termination.
- If pregnancy occurs following the first dose of vaccination, the subsequent doses, if applicable, should be delayed until after pregnancy.

Vaccine immunogenicity, efficacy and effectiveness

Immunogenicity

- HPV vaccines are highly immunogenic; seropositivity after vaccination is close to 100%. Antibody titres are higher with younger age at vaccination². The serological response to vaccine is much stronger than the response after natural infection.
- The high HPV vaccine efficacy seen in clinical trials to date has precluded identification of a minimum protective antibody titre.
- Systematic reviews and one randomized controlled trial have shown seropositivity among subjects who received one dose of HPV vaccine to be non-inferior to that after two or more doses (2, 11).

Efficacy

- For the initial licensure and three-dose schedule, all HPV vaccines have been found to have high efficacy in an HPV-naïve population in studies that used HPV disease endpoints – i.e. cervical intraepithelial neoplasia grade 2 or worse (CIN2+), adenocarcinoma in situ (AIS), and high-grade, vulvar and vaginal lesions – approaching or equalling 100% (12, 13, 14).
- Subsequent studies evaluating two doses in young people aged 9–14 years versus three doses in 15–26-year-olds (prompted by post-hoc analyses of trials in which not all subjects completed a three-dose schedule) showed non-inferiority in seroconversion and geometric mean titres in a two-dose schedule group (15).
- Several studies have shown high efficacy against HPV persistent infection of a single-dose vaccination schedule comparable to a multi-dose schedule (2, 16).

Effectiveness

- Effectiveness data from post-licensure studies involving more than 60 million individuals show that the prevalence of HPV 16 and HPV 18 decreased significantly – by 83% among girls aged 13–19 years and by 66% among women aged 20–24 years – after 5–8 years of vaccination programme (17). There is evidence of indirect protection of unvaccinated females through herd protection effects (18).
- Data for bivalent Cervarix™ vaccine from one population study showed 86% effectiveness against CIN3+ for females vaccinated at 12–13 years of age, and 51% for those vaccinated at the age of 17 years (19). Quadrivalent Gardasil® data using demographic and health register to follow over 1 million females aged 10–30 years show 88% lower risk against invasive cervical cancer for those vaccinated before 17 years of age compared with those who had never been vaccinated (20). An observational study using population-based cancer registry data for women up to 30 years of age shows that the introduction of bivalent Cervarix™ in the national immunization programme resulted in near-elimination of cervical cancer among women who were vaccinated at 12–13 years of age (21).
- In several countries, substantial decreases in cases of genital warts have occurred following the introduction of quadrivalent HPV vaccine in the national immunization programme, with reductions observed in unvaccinated young men in settings with female-only programmes, indicating herd protection.
- Vaccine-induced HPV type replacement is deemed unlikely although it is still too early to preclude it.

² The age extension of original licensure of HPV vaccines to pre-adolescent and adolescent girls and boys – in whom efficacy trials were not deemed feasible because of ethical considerations – was granted on the basis of immunobridging studies demonstrating non-inferiority.

Table 4 summarizes information on immunogenicity and efficacy for multi and single-dose schedules.

Table 4. Immunogenicity and efficacy of prequalified HPV vaccines

Vaccine	Bivalent			Quadrivalent	Nonavalent
Trade name	Cecolin®	Cervarix™	Walrinvax®	Gardasil®	Gardasil-9®
Immunogenicity	All highly immunogenic (minimum antibody titre for protection not established)				
Efficacy (studies using disease endpoints in naïve population, except for Cecolin®)	97.7% (95%CI 86.2–99.9); persistent infection >6 months) 95.3% (95%CI 70.7–99.9; persistent infection >12 months) (5)	81% (95%CI 53–94, for CIN2+) (22) 93% (95%CI 79–99, for CIN3+) (23)	79% (95%CI 23–96) for CIN2+ (21)	98% (95%CI 93–100, for CIN2+) (24) >90% (for vulvar and vaginal lesions) (23)	Little or no difference compared to quadrivalent Gardasil® for types targeted by both vaccines, 96.7% for 5 additional types (5)
Availability of 1-dose efficacy or immunobridging ³ data	Efficacy inferred through immunobridging (25)	Efficacy data available (26)	Immunobridging study planned	Efficacy data available (27)	Efficacy data available ³

³ Definition: GMT levels at 6- and 24-months non-inferior to a product with 1-dose efficacy data

Cross-protection

- Data suggest that bivalent and quadrivalent HPV vaccines provide partial cross-protection against HPV types not included in the vaccine. More consistent and higher cross-protection against prevalent infection with HPV types 31, 33 and 45 has been observed in countries that introduced bivalent Cervarix™ vaccine than in countries using quadrivalent Gardasil®. A review concluded that, compared to direct protection against HPV types included in the vaccines, cross-protection is inconsistent and wanes over time (28). The extent of cross-protection for Cecolin®, Walrinvax® and Gardasil-9® is not yet known.

Duration of protection

- With a multi-dose schedule, antibody titres remain high for at least 12 years for the bivalent Cervarix™ and quadrivalent Gardasil® vaccines, and at least 6 years for the more recently licensed Gardasil-9® vaccine. For a single-dose schedule, antibody titres have shown to be stable for at least 10 years (15).
- In a post-hoc analysis comparing one-, two- and three-dose schedules, vaccine efficacy was high (>90%) against HPV 16/18 for at least 10 years post-vaccination for all schedules.
- There is no evidence to suggest that a booster dose is needed after primary HPV vaccination.

Programmatic considerations

- Several programmatic characteristics are similar or identical across the HPV vaccine products (e.g. administration, formulation, storage temperature, vaccine vial monitor, wastage rate).
- Other important factors – such as presentation, CTC indications, cold chain and storage requirements, doses per container, and price – differ by product and may require additional planning for countries choosing to switch or to incorporate multiple products (Table 5).
- The primary target population for HPV vaccination is girls aged 9–14 years. Secondary target populations such as females ≥15 years of age, boys, older males or men who have sex with men, are recommended to be vaccinated only if this is feasible and affordable. Not all currently available products are licensed for boys.
- Supply availability and cold chain implications should be considered when planning catch-up vaccination of multi-age cohorts up to 18 years of age at the time of introduction.
- Training of immunization staff is required for use of all HPV vaccine products prior to introduction, including in situations where the correct application of the multi-dose vial policy should be undertaken before switching to a product with 2-dose vial presentation.

Presentation, storage requirements and packaging details for prequalified HPV vaccines are included in Table 5.

Table 5. Storage and packaging characteristics of prequalified HPV vaccines

Vaccine	Bivalent			Quadrivalent	Nonavalent
Trade name	Cecolin®	Cervarix™	Walrinvax®	Gardasil®	Gardasil-9®
Presentation * and dosage	Liquid, ready to use 1-dose vial (0.5ml/dose)	Liquid, ready to use 1- and 2-**dose vial (0.5 ml/dose)	Liquid, ready to use 1-dose vial (0.5ml/dose)	Liquid, ready to use 1-dose vial (0.5 ml/dose)	
Vaccine vial monitor	Type 14	Type 30	Type 14	Type 30	Not included
Storage temperature and shelf-life	At +2 to +8 °C: 36 months	At +2 to +8 °C: 60 months	At +2 to +8 °C: 24 months	At +2 to +8 °C: 36 months	
Stability and CTC***	-	From +8 to +25 °C: 3 days; from +25 to +37 °C: 1 day	-	From +8 to +40 °C: 4 days (CTC) From +8 to +42 °C: 3 days (CTC)	
Cold chain volume/dose (secondary packaging)	Carton containing: 10 vials – 14.29 cm ³	Carton containing: 1 vial – 28.8 cm ³ 10 vials – 5.7 cm ³ 100 vials – 4.8 cm ³	Carton containing: 20 vials – 11.8 cm ³	Carton containing: 1 vial – 75 cm ³ 10 vials – 15 cm ³	Carton containing: 10 vials, supplied by a) UNICEF – 18.4 cm ³ b) PAHO – 15.11 cm ³

*Pre-filled single-dose syringes are also commercially available for Cervarix and Gardasil HPV vaccines.

**Any unused vaccine in opened 2-dose vials should be discarded six hours after opening or at the end of the immunization session, whichever comes first (29).

*** Controlled temperature chain (30)

Two-dose schedule

- Can be used from 9 years of age until the maximum age for which the products are licensed with a suggested interval of 12 months for programmatic and efficiency reasons.
- Minimum interval between doses: 6 months.
- There is no maximum interval between doses; if programmatically opportune, longer intervals up to 3 or 5 years can be considered.

Alternative, single-dose schedule

- Can be used in females and males aged 9–20 years.
- Given the current evidence of comparable efficacy and duration of protection to a two-dose schedule, a one-dose schedule may offer programme advantages, be more efficient and affordable, and contribute to improved coverage.

- From a public health perspective, the single-dose schedule can offer substantial benefits that outweigh the potential risk of lower levels of protection if efficacy wanes⁴ over time.

Schedule for immunocompromised persons

- Multi-dose schedule is recommended for immunocompromised or HIV-infected persons (regardless of age or antiretroviral therapy status):
 - at least two doses with a minimum interval of 6 months between the first and the second dose (0, 6);
 - where possible, three doses with a 0, 1–2, 6 months dosing schedule.

Interchangeability

- The same HPV vaccine product should be used in multi-dose vaccination schedules.
- If the product used for the prior dose(s) is unknown or unavailable, any HPV vaccine can be administered to complete the recommended schedule.
- Data are available on safety and immunogenicity of a mixed schedule combining Gardasil-9® and Cervarix™ (2).

Co-administration with other vaccines

- HPV vaccines can be co-administered with other vaccines (including live vaccines) at the same visit, using a separate syringe at a different anatomical site (2).

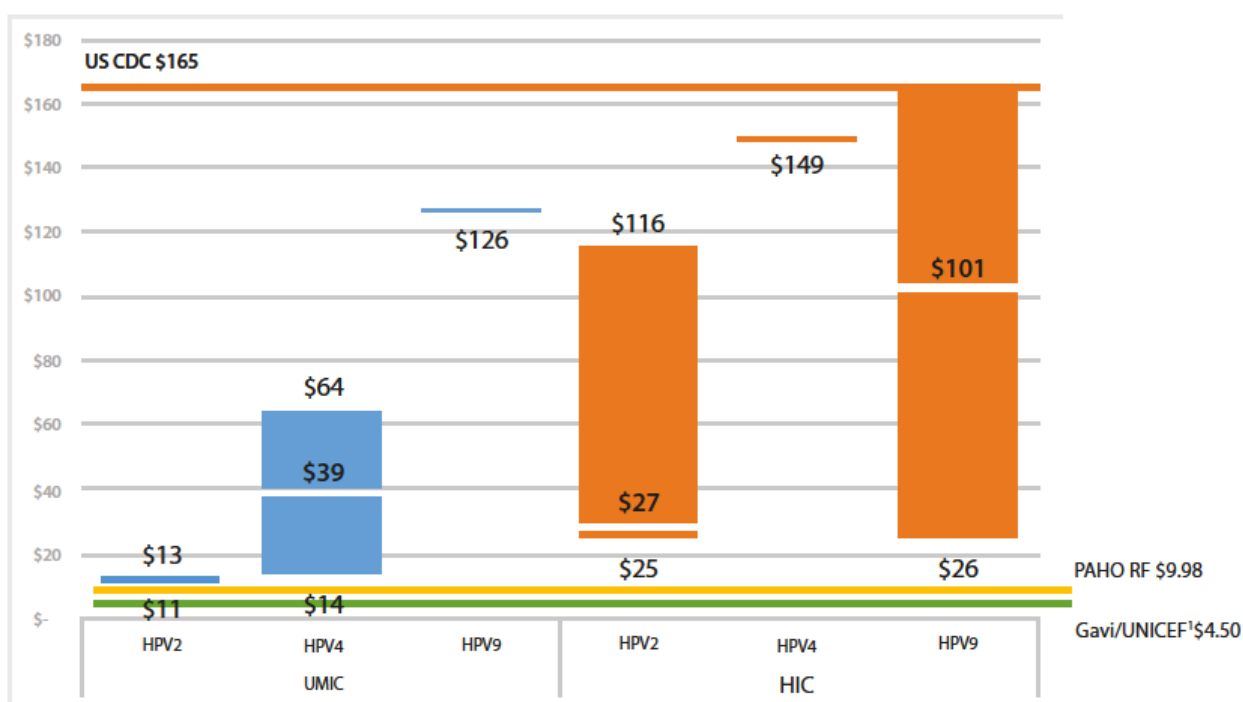
Cost and financial considerations

- HPV vaccine pricing varies by product, presentation, procurement mechanism and country income group. The median prices for self-procuring middle-income countries (MIC) and high-income countries (HIC) are significantly higher than the prices of Gavi and the PAHO Revolving Fund.
- In 2021, the MIC median price for quadrivalent HPV vaccine was US\$ 39 per dose, while the HIC median price for bivalent HPV vaccine was US\$ 27 and for nonavalent vaccine was US\$ 101 (31). Figure 1 below includes reported price per dose of HPV vaccine by procurement method and income group according to MI4A purchase data (32).
- Indicative current Gavi prices (33) for HPV vaccines that can be used for budgeting purposes are: US\$ 2.90 per dose for Cecolin®, US\$ 5.18 per dose for Cervarix™, and US\$ 4.50 per dose for quadrivalent Gardasil®.
- The WHO Cervical Cancer Prevention and Control Costing tool (C4P) on HPV vaccine has been developed to support countries to plan for introducing HPV vaccine into an existing immunization programme (34). There is a dedicated costing tool for calculating the cost of switching products (35).

⁴ There is no current evidence of waning efficacy over time.

- Several studies indicate that, at current vaccine prices and recommended schedules, girls-only vaccination compared with no vaccination is cost-effective, even when no cross-protection or herd protection is assumed (36). To assess cost-effectiveness in the national context, the PRIME tool can be used (37).

Figure 1. Price per dose HPV vaccines by procurement methods and income group (Source: WHO HPV Global Market Study, April, 2022)



Median values in bold.

Source: 2021 MI4A Purchase Data (country-reported).

Note: Reduction in Gavi/UNICEF price is the result of new products being available. Gavi/UNICEF will pay this price when countries elect to introduce the relevant product into their national immunization systems.

PAHO RF= Pan American Health Organization Revolving Fund

Availability and supply

- WHO monitors the global HPV vaccine market and publishes regular updates. According to the latest report (2022) (38) the global supply is expected to improve and reach a healthy situation in the mid-term (2024-2026). Currently, given a limited buffer, careful phasing of multi-age cohort campaigns and countries' willingness to use any of the available HPV vaccines, are the most critical elements for ensuring that all countries can access supply.

- Widespread adoption of (off-label) single-dose schedule can lead to improvement of the supply–demand balance in the short term but may have an impact on the sustainability of the HPV market in the medium and long term.
- All manufacturers require a six-month lead time from purchase order to in-country delivery.

Prioritization of new vaccine introduction decisions

The WHO CAPACITI tool (39) is available to support standardized country decision-making and comparison of multiple product choice options for introduction, product switch, or changes of schedule. The tool allows for evidence and different stakeholder views to be combined in order to come to a recommendation and document both processes and outcomes.

Inclusion of HPV vaccine into the National Immunization Strategy

Countries may consider the introduction or switch of HPV vaccine products as part of the prioritization process and in the broader context of immunization planning within the National Immunization Strategy (NIS) (40). The NIS is designed for better integration of immunization with other health interventions, universal health coverage targets and national planning cycles and focuses on long-term goals with intermediate objectives and prioritized strategies.

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