

GLOBAL MARKET STUDY

HPV

Key Takeaways

- Sixteen years after the first marketing authorisation, 60% of WHO Member States have introduced human papillomavirus (HPV) vaccine into their national routine immunization schedule. However, as of 2021, only 13% of girls in the world are fully protected.
- High interest in HPV vaccination by countries across all income groups has led to a sharp increase in demand in the past several years. However, a combination of factors, primarily linked to continued supply constraints, has slowed the pace of introduction, particularly in low-resource settings.
- In the past year, the risk of HPV shortages has significantly decreased, mainly because of active demand management (in response to past supply shortages), delays in programme implementation driven by the coronavirus disease (COVID-19) pandemic and availability of additional supply resulting from increased production capacity. In addition, two new HPV vaccines achieved marketing authorization. One of these has also received WHO prequalification.
- Despite global supply now being sufficient to meet global demand, over the next 3 years access constraints at the individual country level may continue to occur due to limited supply buffers. Careful phasing of multi-age cohorts (MACs) campaigns, particularly in large countries, and country willingness to accept all available HPV vaccines will be critical to minimize the risk of shortages. Implementation of large catch-up campaigns in older-age cohorts and widespread implementation of boys' vaccination will also require attention.
- By 2024, sufficient increases in production capacity will result in a healthy HPV supply situation. This outcome is subject to the success and timing of the clinical development programmes currently in advanced stages as well as completion of manufacturing capacity increases from existing HPV vaccine manufacturers.
- In the long term, HPV supply will not only be sufficient to meet the goals of the Global Strategy to Accelerate the Elimination of Cervical Cancer, but also to significantly outstrip global demand for HPV vaccines. Consequently, active engagement with all manufacturers and management of future supply and demand will be required to ensure market sustainability.
- The potential widespread adoption of a one-dose schedule would lead to higher supply flexibility in the short-term. In the mid-term, it could result either in expansion of the HPV programs (i.e., boys or older age cohorts) or the rapid reduction in programmatic dose requirements. The latter would require careful management to ensure continuity of supply and access.

QUICK STATS

NUMBER OF VACCINE SUBTYPES¹

3

NUMBER OF VACCINE PRODUCTS

5

TOTAL NUMBER OF MANUFACTURERS²

4

2022 ESTIMATED GLOBAL SUPPLY³

~80M DOSES (MAXIMUM)

2022 ESTIMATED GLOBAL DEMAND⁴

~80M DOSES

2021 REPORTED PRICE PER DOSE (RANGE)⁵

US\$ 4.50 TO US\$ 196.32

- 1 Vaccine subtypes are differentiated by the antigen content of the various HPV vaccines; in this case, three distinct vaccine subtypes are available on the market: HPV2 (16, 18), HPV4 (6, 11, 16, 18) and HPV9 (6, 11, 16, 18, 31, 33, 45, 52, 58).
- 2 The total number of manufacturers indicates only the companies that have full manufacturing capacity. The number does not include licensors providing a portion of the manufacturing process (e.g., filling and finishing) or distributors that simply commercialize the product in some locations.
- 3 Supply refers to the "available supply for commercialization", defined as the number of doses available for sale at the global level in one typical year with normal production facility utilization across the various vaccines (not factoring in special market, regulatory or technical events). This differs from the manufacturing capacity or the plant yearly throughput.
- 4 Demand refers to "programmatic dose requirement", defined as the average estimated number of doses a country would need to procure to meet its immunization programme needs, whether these are routine or campaign. This requirement includes wastage (depending on the presentation) and buffers.
- 5 The highest publicly reported price is the private market price posted by the US Centers for Disease Control and Prevention (US CDC) (<https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html>, accessed 20 March 2022).

Disclaimer: This market study incorporates the impact of the COVID-19 pandemic on the HPV vaccination programme. Demand projections assume that programmatic delays or disruptions will be fully absorbed and resolved by 2023.

Purpose & Background

Following the adoption by WHO Member States of a global strategy to accelerate the elimination of cervical cancer in November 2020, increasing introduction and coverage of HPV vaccine worldwide is essential to meeting its targets. Since 2018, WHO has established ongoing monitoring of HPV vaccine supply and demand via the Market Information for Access to Vaccines (MI4A) initiative to help inform decisions, shaping policy, programmes and markets in the face of access challenges.⁶

This study provides the most up-to-date understanding of current and future global trends and drivers of HPV supply and demand to support the resolution of challenges to equitable, unrestricted and flexible access to HPV vaccines across all regions and income groups.

Market Highlights

As of March 2022, 117 countries (60% of WHO Member States, corresponding to approximately one-third of the global target population) have introduced HPV vaccine into their national routine immunization schedules, with 10 new introductions planned by the end of 2022. The rate of introduction (Figure 1) in low and middle-income countries (LICs and MICs), which carry the greatest share of disease burden,⁷ remains lower than in high-income countries (HICs). Approximately half of the countries (47%)⁸ that have introduced the HPV vaccine are self-procuring. Based on MI4A demand estimates for 2022, approximately 10% of global demand is for use in boys.

Currently, five HPV vaccines have received marketing authorisation and/or WHO prequalification:

- Three bivalent (HPV2) vaccines:
 - » GSK's Cervarix® with proprietary AS04 adjuvant, indicated for girls and women, boys and men between 9-45 years of age.
 - » Inovax's Cecolin® with aluminium-containing adjuvant, indicated for girls and women aged 9-45 years.
 - » Walvax Biotechnology's product with aluminium-containing adjuvant, indicated for girls and women aged 9-30 years (developed by its subsidiary Shanghai Zerun Biotech).
- One quadrivalent (HPV4) vaccine: Merck's Gardasil® with aluminium-containing adjuvant, indicated from 9-45 years of age for girls and women, boys and men.
- One nonavalent (HPV9) vaccine: Merck's Gardasil 9® with aluminium-containing adjuvant, indicated from 9-45 years of age for girls and women, boys and men.

Merck's products represent the great majority of doses procured and have also been commercialized by two licensees: Instituto Butantan in Brazil and Sinergium Biotech in Argentina. Distribution agreements exist in various other countries.

According to the WHO position paper on HPV vaccines, "current evidence suggests that from the public health perspective the bivalent, quadrivalent and nonavalent vaccines offer comparable immunogenicity, efficacy and effectiveness for the prevention of cervical cancer, which is mainly caused by HPV types 16 and 18".⁹

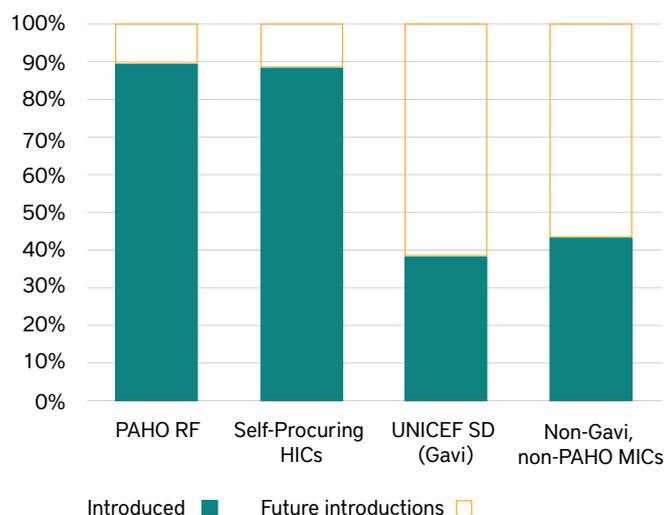
6 In October 2019, SAGE provided guidance to countries regarding the management of the available HPV vaccine supply to limit access constraints. Meeting of the Strategic Advisory Group of Experts on Immunization. Source: Wkly Epidemiol Rec. 2019;94(47):541-60 (<https://apps.who.int/iris/handle/10665/329962>, accessed 22 March 2022).

7 HPV cases (all cancers), women (2018). Source: Global Cancer Observatory In: International Agency for Research on Cancer; Global Cancer Observatory [website]. Lyon: IARC; 2022 (<https://gco.iarc.fr>, accessed 22 March 2022).

8 Procurement status of countries informed by 2013-2021 JRF purchase data.

9 Human papillomavirus vaccines: WHO position paper. Wkly Epidemiol Rec. 92(19):241-68 (<https://apps.who.int/iris/handle/10665/255354>, accessed 22 March 2022).

FIG. 1: HPV VACCINE INTRODUCTION STATUS BY COUNTRY PROCUREMENT GROUP



PAHO RF: Pan American Health Organization Revolving Fund, HICs: high-income countries, UNICEF SD (Gavi): 73 countries eligible for support by Gavi, the Vaccine Alliance;; MICs: middle-income countries;

Global Demand (Programmatic Doses Requirements)

A global demand forecast for HPV vaccine has been developed for the 10-year period 2022–2031 based on historical procurement data and the latest available information on country introduction plans and other key drivers of demand (e.g. coverage increases and planned MAC campaigns). The base-case scenario of the forecast was developed based on the current WHO-recommended two-dose schedule for girls under 15 years of age.¹⁰ The scenario assumes planned MAC campaigns and continuation of current or near-term planned introductions in boys and older age cohorts; no new MAC campaigns, boys or older-age cohort introductions are included to reflect the 2019 Strategic Advisory Group of Experts on Immunization (SAGE) recommendation to “temporarily pause implementation of boy, older age group (>15 years) and multi-age cohort (MAC) HPV vaccination strategies until vaccine supply allows equitable access to HPV vaccine by all countries.”¹¹

10 Human papillomavirus vaccines: WHO position paper. Wkly Epidemiol Rec. 92(19):241–68 (<https://apps.who.int/iris/handle/10665/255354>, accessed 22 March 2022).

11 In the same context, SAGE also proposed two alternative approaches to countries, subject to consideration of context and programmatic feasibility: (i) to retain the accelerated impact of MAC campaigns, target girls who are 13 or 14 years old or in the equivalent school grade for two-dose vaccination; or (ii) to temporarily further reduce vaccine supply needs, adopt a 3- to 5-year extended interval between the two doses when the first dose is delivered at 9–10 years of age. This latter strategy constitutes off-label use of the vaccine. Meeting of the Strategic Advisory Group of Experts on Immunization. Wkly Epidemiol Rec. 2019;94(47):541–60 (<https://apps.who.int/iris/handle/10665/329962>, accessed 22 March 2022).

Global HPV programmatic dose requirements for 2022 will total ~80M doses, including demand from the public and private sectors. Without any supply-related constraints, demand is projected to exceed 130M doses in 2023,¹² reaching ~140M doses in 2026 and stabilizing at ~125M doses by 2031 once MAC campaigns are completed. In the short term, increased demand is expected to be largely driven by potential Gavi-supported MAC campaigns and planned catch-up activities for MACs campaigns in several large HICs.¹³ In the medium term, introductions in the national immunization programmes of China and India (estimated for 2024 and after) are expected to drive the most significant increases in global demand; the combined demand of these countries will represent approximately one-third of the market by 2031.

Over the past several years, MI4A has been simulating different scenarios to assess the potential evolution of global demand under different policy options. The most relevant scenarios for ongoing policy and programmatic discussions are shown in Fig. 2.¹⁴

- A. The single dose with single-dose MAC scenario¹⁵ provides insight into the implications of potential policy recommendations for a one-dose schedule on programmatic dose requirements in the short, medium and long term. This scenario results in the lowest dose requirements among the evaluated scenarios, with required doses stabilizing at ~70M in 2028.
- B. The scenario detailing a global switch to a one-dose HPV schedule accompanied by a shift to a boys vaccination strategy in all countries assesses the potential use of the available supply to reach a broader target population; programmatic dose requirements in the medium and long term are comparable to the base demand scenario.¹⁶

12 While this projection represents the best estimate of unconstrained demand, it does not correspond to full potential demand for the year; the persistence of supply constraints has already led to postponement of country introductions and MAC campaigns in the past (demand that is now forecasted for subsequent years).

13 A minimum of 24 Gavi-supported countries are forecast to conduct MAC campaigns by 2025– only planned Gavi MAC campaigns are included in the base demand forecast.

14 Scenarios were developed to give an indication of possible global programmatic dose requirements and do not represent WHO’s endorsement of specific schedules in specific groups of countries. All scenarios assume that all countries have introduced the HPV vaccine by 2030 and that MACs are implemented only for vaccination of girls.

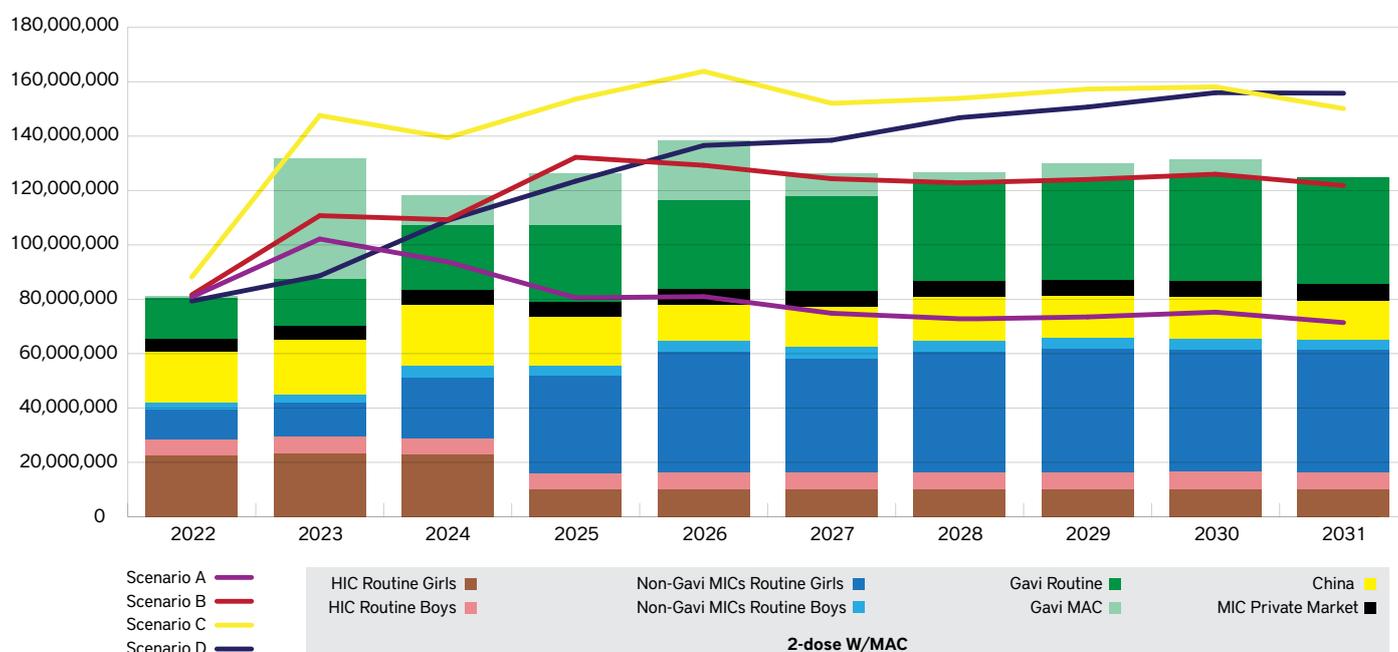
15 The single dose with MAC scenario models a single-dose schedule with increased coverage for all countries. LICs and LMICs are assumed to adopt the single-dose schedule in 2023, and UMICs (upper-middle-income countries) and HICs are assumed to switch in 2025.

16 The single dose with MACs and switch to gender-neutral programme scenario follows the same assumptions as the single dose with MACs scenario. The only exception is that countries adopt a gender-neutral strategy in the year during which a single-dose schedule is implemented.

C. The largest programmatic dose requirements in the short and medium term are required in the scenario that combines the continuation of a two-dose schedule with the implementation of a boys vaccination strategy in all HICs and MICs, including China and India.¹⁷

D. The programmatic dose requirements to support WHO’s cervical cancer elimination goals by 2030¹⁸ are the highest in the long term due to rapid increases in HPV coverage required in all countries,¹⁹ resulting in an additional ~25M doses per year by 2030.

FIG. 2: COMPARISON OF UNCONSTRAINED DEMAND SCENARIOS



Gavi: Gavi, the Vaccine Alliance; HIC: high-income country; MAC: multi-age cohort; MICs: middle-income countries.

Global Supply (Available Supply for Commercialisation)

Consultations with manufacturers and experts, as well as a review of publicly available information on HPV vaccines, provided the basis for an assessment of the current and future global supply of HPV vaccine.

Since the last update, one new HPV vaccine – Cecolin, a bivalent HPV vaccine produced by Inovax – has received WHO prequalification, expanding the global supplier base from two to three suppliers. In addition, Walvax Biotechnology’s product received marketing authorization and existing manufacturers are continuing investments to increase manufacturing capacity. Supply has already

increased on average by 15% annually in recent years, and new investments are expected to translate into continuing and increased growth in available supply, with significant increases anticipated in the short and medium term (2023–2025).

Two quadrivalent HPV vaccines are currently in Phase 3 clinical development: one from Serum Institute of India and one from the China National Biotech Group (CNBG). All use aluminium-containing adjuvants and are likely to be licensed with an indication for girls 9–14 years old for two- and/or three-dose schedules. The success, timing and capacity of these pipeline vaccine efforts will have a significant impact on the long-term outlook for HPV vaccine supply.

17 The two-dose routine with MAC and switch to gender-neutral programme scenario follows the same assumptions as the base scenario, with the exception that a gender-neutral strategy is implemented from the year of HPV introduction.

18 Modelling the potential increase in demand from the global cervical cancer elimination strategy assumes HPV vaccine introductions across the globe, with all countries reaching at least 90% coverage by 2030.

19 The elimination scenario follows the same assumptions as the base case (two-dose schedule) but estimates that all countries will reach at least 90% coverage by 2030; no MAC is included in this scenario ([https://www.who.int/news-room/events/detail/2019/10/08/default-calendar/strategic-advisory-group-of-experts-on-immunization-\(sage\)-october-2019](https://www.who.int/news-room/events/detail/2019/10/08/default-calendar/strategic-advisory-group-of-experts-on-immunization-(sage)-october-2019), accessed 20 March 2022)

The base projection foresees a threefold increase in available supply over the medium term (4–6 years, range 2–4X), from the ~80M doses expected to be available in 2022.

Technology transfers for HPV vaccine are limited. Currently, Merck supplies Instituto Butantan and Sinergium Biotech with HPV drug substance, and each supplier performs the subsequent filling and finishing processes. Both suppliers commercialize the HPV vaccine in Brazil and Argentina, their respective domestic markets. Additional technology transfers involving companies in Russia and Thailand are currently being implemented; the timing and likelihood of these activities contributing to global supply are unclear.

Supply–Demand Balance

In past years, continuing supply constraints particularly affected LICs and MICs and led to the adjustment of introduction plans, especially in Gavi-supported countries, and to the issuing of adapted global policy recommendations. As result of this proactive management of HPV demand, along with declines in immunization coverage because of the COVID-19 pandemic, and increases in the available HPV supply, primarily from one of the existing manufacturers, the supply–demand balance has significantly improved.

Starting from 2022, global supply is expected to be sufficient to meet base demand for a two-dose routine programme²⁰ targeting girls, inclusive of MACs campaigns (Fig. 3). Nevertheless, given limited buffers, for the next 2–3 years careful phasing of MAC campaigns and country willingness to use any of the available HPV vaccines will be necessary conditions to ensure all countries can access the supply required to achieve the primary goals of the HPV vaccination programme. Attention will also be required to the supply implications of implementing large catch-up campaigns in older-age cohorts and to the widespread adoption of boys vaccination strategies.

The supply–demand balance is expected to **steadily improve from 2023 to 2024, subject to the realization of the following conditions:**

- » Sustained committed to existing programmes by existing suppliers, success in expanding capacity and making new capacity available (both in terms of the timing and size of the capacity increases); and
- » Successful completion of clinical development programmes by pipeline manufacturers, obtaining required marketing authorisation and making supply available in the expected quantities in all countries where necessary.

The expected increases will improve the flexibility of supply and allow countries more freedom of choice in term of products and vaccination strategies. After 2025, HPV vaccine supply is expected to significantly exceed demand even in the most pessimistic supply scenarios. Therefore, active engagement with all manufacturers and management of future supply and demand will be required to ensure market sustainability.

In this context, the potential adoption of a one-dose schedule would further improve the supply–demand balance in the short term, allowing accelerated implementation of MAC campaigns and more flexibility on product choice. In the medium and long term, the implementation of a one-dose schedule by a large number of countries could (i) either allow for a more generalized adoption of boys and/or older cohorts vaccination strategies or (ii) lead to a rapid reduction in programmatic dose requirements. The latter, coupled with the fact that not all products have data available supporting the switch to one dose or boys vaccination, could impact the sustainability of the HPV market for vaccine manufacturers, including through price changes and/or market exits. Transition to a one-dose schedule would therefore require carefully management, including through generation of evidence for single-dose efficacy for all products.

FIG. 3: SUPPLY/DEMAND BALANCE^{21,22}

Demand Scenarios	Base supply			Low supply			Legend
	Short-Term (1-3)	Mid-Term (4-6)	Long-Term (6-9)	Short Term (1-3)	Mid Term (4-6)	Long-Term (6-9)	
2-doses +2ds MACs (base case)	Green	Green	Green	Red	Yellow	Green	<ul style="list-style-type: none"> ■ Excess supply Supply >2X Demand ■ No risk of shortages Supply >1.3X Demand ■ Some risk of shortages Supply <1.3X Demand ■ Insufficient supply Supply <1.1X Demand
2-doses +2ds MACs & gender neutral	Red	Green	Green	Red	Red	Yellow	
2-doses no MACs high coverage (Elimination)	Green	Green	Green	Yellow	Green	Green	
1-dose +1d MACs	Green	Green	Green	Green	Green	Green	
1-dose +1d MACs & gender neutral	Yellow	Green	Green	Red	Green	Green	
	Green	Green	Green	Green	Green	Green	

1d: one dose; 2ds: two doses; MACs: multi-age cohorts.

20 In this scenario, boys’ vaccination is not expanded further to countries other than the ones that already have them in place.

21 Low supply scenario based on more conservative assumptions concerning manufacturing capacity increases and success in clinical development.

22 One-dose-only scenarios assume that supply is available solely from suppliers that have supporting data for a single-dose schedule.

Price

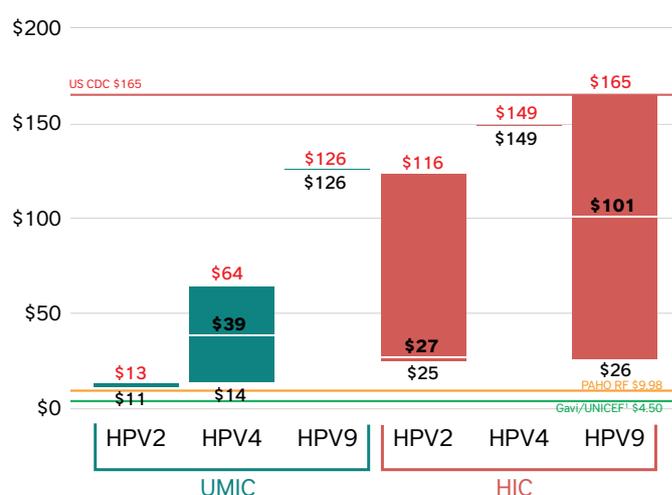
The reported price per dose²³ of HPV vaccines shows a tiered structure by procurement method and income group (Ref. Figure 4), with UNICEF (United Nations Children’s Fund) Supply Division (SD)/Gavi and the PAHO (Pan American Health Organization) Revolving Fund (RF) paying the lowest prices, at US\$ 4.50 and US\$ 9.98,²⁴ respectively. The UNICEF SD/Gavi price for GSK’s HPV2 product will increase to US\$ 5.18 starting in 2022, and the price for Merck’s HPV4 will continue at US\$ 4.50 until 2025. Contracted price for Inovax starting in 2022 is \$2.90 per dose though no country is yet to procure the vaccine. The self-procuring MICs’ median price for HPV2 is more than twice the Gavi price and slightly higher than the PAHO price. HPV4 median price is instead significantly higher.

Generally, GSK’s HPV2 product is lower priced, ranging from US\$ 11.17 to US\$ 12.53, compared with Merck’s HPV4 product, which ranges from US\$ 13.81 to US\$ 64.16 for self-procuring MICs.²⁵ HPV prices have generally decreased across all procurement and income groups over the last half-decade. Further reductions in price are expected to materialize as and when a more competitive environment is established by future new market entrants, provided there is reasonable demand for those new products.

Affordability remains a concern for MICs that no longer are or never were supported by Gavi or PAHO RF. Both Merck and GSK have made price commitments (under specific conditions) to countries transitioning out of Gavi support.²⁶ Some countries are no longer eligible for these time-limited commitments.²⁷

The overlap between the reported prices paid by MICs and those paid by HICs indicates space for improvement towards a more equitable tiered pricing. In the context of the current global economic uncertainty and of the ambitious agenda of reaching zero-dose children in the Immunization Agenda 2030 (IA2030), country financing for immunization will be stretched by both vaccine procurement and implementation costs. The impact of HPV vaccine introduction on health and immunization budgets can represent a significant barrier, particularly in countries where HPV vaccine represents a substantial financial burden.

FIG. 4: 2021 HPV SELF-PROCURED PRICE PER DOSE



HPV: human papillomavirus; PAHO: Pan American Health Organization; UMIC: upper-middle-income country; US CDC: US Centers for Disease Control and Prevention; WAP: weighted average price.

- 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.

23 WHO JRF 2021 data.

24 The PAHO RF price is the 2021 price for HPV4.

25 Excluding outliers.

26 For details of price commitments, see the fact sheet on vaccine pricing for Gavi-transitioning countries: <https://www.who.int/publications/m/item/factsheet-on-vaccine-pricing-for-gavi-transitioning-countries>.

27 As part of its 5.0 strategy (2021–2025), Gavi is outlining parameters for potential engagement with former Gavi-eligible countries and non-Gavi-eligible countries with gross national income per capita of up to US\$ 6000 to support introduction of new vaccines, including HPV. This support would facilitate introduction of HPV in MICs but is not expected to come into play before 2022.

Areas for Action

Careful coordination and investments are required to enhance supply availability towards global cervical cancer elimination goals. Specific actions are recommended as follows:

- ✓ WHO and its partners will continue to convene a global access dialogue engaging all stakeholders to achieve equitable access to supply, including through active management of demand and supply and implementation of WHO recommendations.
- ✓ WHO will continue to explore opportunities to increase access through timely translation of emerging scientific evidence into policy recommendations, particularly with reference to the comparability of immunogenicity, efficacy and effectiveness of the available quality-assured products and on optimized schedules (e.g. one-dose).
- ✓ WHO will continue providing timely support for prequalification of new HPV vaccines and seamless implementation of post-marketing changes of relevance for the programme (e.g. one-dose, boys vaccination).
- ✓ WHO will continue to inform country decision-making regarding HPV vaccine product selection and adoption of WHO recommendations to improve flexibility of demand and support implementation of HPV programmes that can be sustainably financed.
- ✓ WHO and its partners will work with MICs in line with IA2030 and the Gavi 5.0 MICs approach to support introduction of HPV vaccine.

For more information, contact:
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Methodology & Sources

MI4A Technical Advisory Group of Experts:

MI4A benefits from the expertise of a standing advisory group for input, review and validation of market analyses. The group includes members from regional technical advisory groups on immunization, UNICEF SD, PAHO RF, Gavi, the Bill & Melinda Gates Foundation, implementation partners and WHO SAGE, along with manufacturers' associations (the Developing Countries Vaccine Manufacturers Network and the International Federation of Pharmaceutical Manufacturers and Associations) and independent experts.

Supply resources:

MI4A annual data collection from manufacturers, high-level validation of outputs of analysis with studies from Gavi and the Bill & Melinda Gates Foundation, bilateral discussions with manufacturers on capacity drivers and pricing prospects, review of clinical trial information, review of available cost of goods studies, review of manufacturing processes documentation (e.g., the European Medicines Agency), analysis of vaccine products registration.

Demand resources:

Historical procurement: WHO MI4A V3P/JRF (2013–2021) and UNICEF SD (2014–2021). Planned/projected country introductions: WHO Joint Reporting Form (JRF), Gavi Operational Forecast, 2020 WHO Estimates on HPV vaccine coverage, 2020 update (Immunization, Vaccines and Biologicals database, July 2021).

Pricing resources:

WHO MI4A V3P/JRF, PAHO RF, UNICEF SD (2020 data).

Other useful public resources

This global study complements market analysis performed by UNICEF SD and Gavi for specific market segments:

Human papillomavirus (HPV) supply and demand update. New York: UNICEF SD; 2020 (<https://www.unicef.org/supply/reports/human-papillomavirus-hpv-vaccine-supply-and-demand-update>, accessed 20 March 2022).

Supply and procurement roadmap: human papillomavirus vaccine, public summary. In: Gavi/Our alliance [website]. Geneva: Gavi; 2017 (<https://www.gavi.org/sites/default/files/document/hpv-supply-and-procurement--roadmap.pdf>, accessed 20 March 2022).