

GLOBAL MARKET STUDY

HPV

Key Takeaways

- High interest in HPV vaccination programmes by countries across all income groups has led to a sharp increase in demand in the past few years. However, a combination of factors, including supply constraints and country product preferences, has resulted in a slower introduction pace than desired.
- Fourteen years after the first HPV vaccine registration, **57% of WHO Member States have introduced HPV vaccine** into their routine national immunization schedule.
- **By 2024, sufficient increases in production capacity will resolve the supply shortages.** Resolution of the constraints is subject to the success and timing of the clinical development programs as well as increases in manufacturing capacity following investment decisions from current manufacturers.
- Until then, careful calibration of demand will be necessary in line with recent WHO SAGE recommendations, as well as deployment of the limited supply to where it is most needed, serving girls most at risk. **WHO continues to convene a Global Dialogue** as a multilateral discussion forum to facilitate short-term alignment of supply and demand.
- In 2020, WHO Member States have adopted the **Global Strategy to Accelerate the Elimination of Cervical Cancer**. Through national HPV vaccine introductions in all countries and increased coverage, this will lead to an increase in total demand up to 160M doses per year by 2030. Further increases in supply will be required to serve this level of demand.

QUICK STATS

NUMBER OF VACCINE SUBTYPES¹

3

NUMBER OF VACCINE PRODUCTS

4

TOTAL NUMBER OF MANUFACTURERS²

3

2020 ESTIMATED GLOBAL SUPPLY³

~60M doses (maximum)

2020 ESTIMATED GLOBAL DEMAND⁴

~60M doses

2019 REPORTED PRICE PER DOSE (RANGE)⁵

US\$ 4.50–178.00

1 Vaccine subtypes differentiate by the antigen content of the various HPV vaccines; in this case, there are three distinct vaccine subtypes available on the market: HPV2 (16,18), HPV4 (6,11,16,18) and HPV9 (6,11,16,18,31,33,45,52,58).

2 This number indicates only the companies that have full manufacturing capacity and does not include licensed companies providing a portion of the manufacturing process (e.g. filling and finishing) or distributors that simply commercialize the product in some locations.

3 This is the "Available Supply for Commercialisation," defined as the number of doses available for sale at the global level in one typical year with normal production facilities 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 buffer.

5 The highest publicly reported price is the CDC posted private market price. Available at: <https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html>

Disclaimer: This market study was completed before the impact of the SARS-CoV-2 pandemic was fully ascertained. Demand projections are based on the assumption that any delay or disruption will be absorbed and resolved in 2021. Uncertainty on the progression of the pandemic raises the risk that disruptions will extend beyond 2021. An updated analysis of overall HPV supply-demand balance is planned for next year, when more information will be available on the impact of the SARS-CoV-2 pandemic on the HPV programme.

Purpose & Background

Several countries across regions and income groups – in particular Gavi-supported countries – have notified WHO of constraints in their access to HPV vaccines. The issue of affordability has also been raised, particularly by MICs not benefiting from Gavi support.

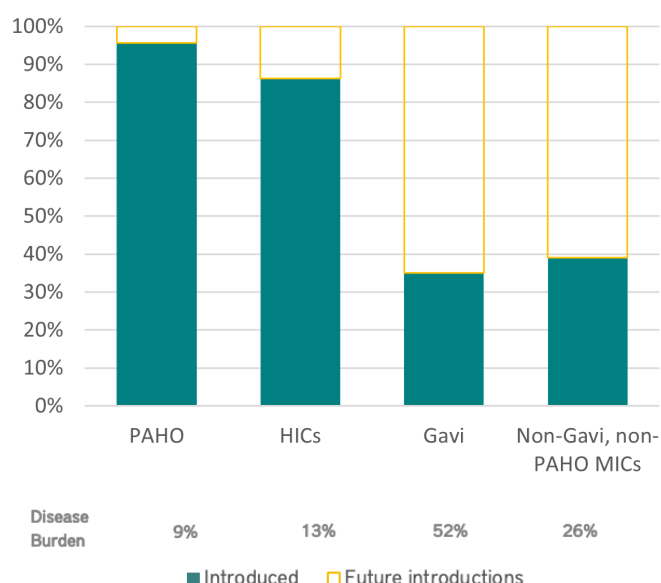
Following the adoption in November 2020 by the WHO Member States of the Global Strategy to Accelerate the Elimination of Cervical Cancer, increasing introduction and coverage of HPV vaccine worldwide will be essential. Since 2018, WHO has established ongoing monitoring HPV vaccine supply and demand via the MI4A initiative. A Global Access Dialogue has been organized by WHO in early 2020 to address the emerging supply constraints through an open engagement with manufacturers, partners and countries.

This study provides the most up-to-date understanding of current and future global trends and drivers of HPV supply and demand. It also identifies actions to help address the current and expected constraints and serves as an important resource for the development of the global cervical cancer elimination strategy.

Market Highlights

As of November 2020, 110 countries (57% of WHO Member States, corresponding to approximately one third of the target population) have introduced HPV into their national routine immunization schedules, with 10 new introductions planned by the end of 2021. The pace of introductions is substantially slower in low- and middle-income countries (LICs and MICs), despite these countries carrying the greatest share of disease burden.⁶ More than two thirds of the countries (69%)⁷ that have introduced the HPV vaccine are self-procuring. Based on MI4A estimates, approximately 17% of the 2020 global demand is for use in boys.

FIG. 1: HPV VACCINE INTRODUCTION STATUS AND DISEASE BURDEN BY COUNTRY GROUP



Currently, four HPV vaccine are registered (three of which have obtained WHO prequalification):

- Two bivalent (HPV2) vaccines:
 - » GSK's Cervarix with proprietary AS04 adjuvant
 - » Inovax's Cocolin with aluminium-containing adjuvant (Not WHO prequalified)
- One quadrivalent (HPV4) vaccine: Merck's Gardasil with aluminium-containing adjuvant
- One nonavalent (HPV9) vaccine: Merck's Gardasil 9 with aluminium-containing adjuvant

Merck's two products are also commercialized by two licensors: Instituto Butantan in Brazil and Sinergium Biotech in Argentina. Distribution agreements exist in various countries.

The WHO position paper on HPV vaccines indicates that "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."⁸ Nevertheless, demand in 2020 is primarily concentrated on HPV4, with an estimated 60% market share by volume, followed by HPV9 (30%) and HPV2 (10%).⁹ Though HPV vaccines make up only ~2% of the global vaccine market by volume, they account for ~15% of global market value (per 2019 JRF purchase data and MI4A estimates).

6 HPV cases (all cancers), women. Source: IARC, Global Cancer Observatory data, 2018.

7 Procurement status of countries informed by 2013–2019 JRF purchase data.

8 Human papillomavirus vaccines: WHO position paper, May 2017, Weekly epidemiological record, N. 19, 12 May 2017. Available at: https://www.who.int/immunization/policy/position_papers/hpv/en/

9 Note that 2% of the market share is unknown (due to lack of procurement data from a small number of countries) and is believed to be split between HPV2 and HPV4.

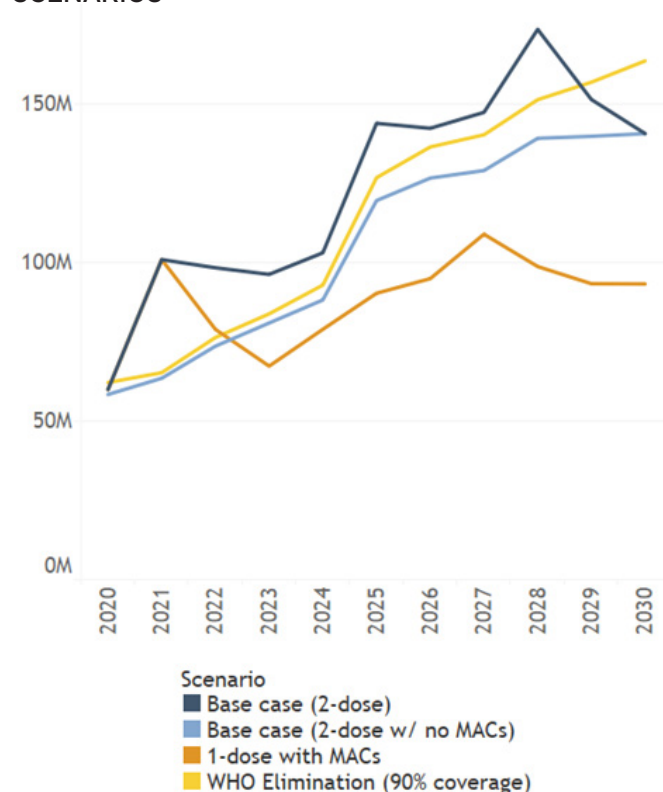
Global Demand

WHO is working to estimate programmatic dose requirements for all key vaccines on the Essential Medicines List. A global demand forecast for HPV vaccine has been developed for the period 2020–2030 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 multi-age cohort [MAC] campaigns). This forecast was developed based on the current WHO-recommended 2-dose schedule for girls under 15 years of age¹⁰ and assumes the implementation of a certain number of MAC campaigns.

Global HPV programmatic dose requirements for 2020 will total ~60M doses including demand from public and private sectors. Demand not constrained by supply will exist in excess of 100M doses for 2021,¹¹ reaching ~170M doses in 2028 and stabilizing at 140M doses by 2030 once MACs are completed. In the short term, demand increases are expected to be largely driven by potential Gavi-supported MAC campaigns.¹² In the mid-term, introductions in China and India to national immunization programmes (estimated for 2023 and after) are expected to drive the most significant increases in demand; their combined demand will represent approximately one third of the market by 2030. Substantial increases in global vaccination coverage due to the global cervical cancer elimination strategy¹³ could result in an additional ~20M doses per year by 2030.

Given the ongoing supply constraints, the Strategic Advisory Group of Experts (SAGE) on Immunization recently recommended to “temporarily pause implementation of gender-neutral, older age group (>15 years) and multi-age cohort (MAC) HPV vaccination strategies¹⁴ until vaccine supply allows equitable access to HPV vaccine by all countries.”¹⁵

FIG. 2: COMPARISON OF UNCONSTRAINED DEMAND SCENARIOS¹⁶



Four scenarios have been developed to assess the potential evolution of global demand under different programmatic options (Figure 2). The scenario with MAC campaigns has the highest short-term programmatic dose requirement. The single-dose scenario results in the lowest doses needed in the mid- and long-term (initial evidence on the efficacy of a single-dose schedule is expected in two years). By 2030, the elimination scenario results in the highest dose requirements of any scenario.

NOTE: The SARS-CoV-2 pandemic is having an impact on HPV vaccine programmatic dose requirement, with mass campaigns and school programmes suspended and catch-up campaigns planned. Further investigation is needed to establish visibility on global vaccine demand in the short- and mid-term.

10 HPV WHO position paper, May 2017.

11 While this represents the best estimate of unconstrained demand, this does not correspond to a 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 the subsequent years).

12 Forty-eight Gavi-supported countries are forecasted to conduct MAC campaigns in the next 10 years. Only planned Gavi MAC campaigns are included in the base demand forecast.

13 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.

14 HICs that have not yet implemented a gender-neutral strategy account for approximately 4M doses per year; planned MAC campaigns over the period 2020–2024 account for approximately 90M doses; estimates of dose requirements from the use of older age group vaccination strategies depends on the age group targeted.

15 In the same context, SAGE also proposed two alternative approaches to countries, subject to consideration of context and programmatic feasibility: (1) to retain the accelerated impact of MAC campaigns, target girls who are 13 or 14 years old or in the equivalent school grade for 2-dose vaccination; or (2) 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 an off-label use of the vaccine. WHO Weekly epidemiological record, 22 November 2019, No 47, 2019, 94, p.541–560.

16 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 all countries introduce by 2030. The “base case” assumes continuation of a 2-dose routine schedule, planned Gavi MAC campaigns, and no new gender-neutral or older age cohorts' introductions. Continuation of current or near-term planned introductions in gender-neutral and older age cohorts are included in the base demand forecast. Base demand with no MAC campaigns is also shown. The “1-dose with MACs” scenario models a single-dose schedule with increased coverage for new introductions in LICs and MICs starting in 2022. Countries that have already introduced and HICs with future introductions are expected to use a 2-dose schedule. The “elimination” scenario follows the same assumptions as the base case (2-dose schedule) but estimates that all countries reach at least 90% coverage by 2030. The elimination scenario assumes no MAC campaigns. <https://www.who.int/immunization/sage/meetings/2019/october/en/> accessed December 8, 2019

Global Supply

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 has been registered – Cecolin from Inovax – expanding the supplier base from two to three suppliers. Additionally, the existing manufacturers are continuing investing to increase capacity; supply has already started increasing in the past few years. However, these new investments will not translate into significant increases in available supply until 2022 at the earliest, given lead times.

Three products are currently in phase III clinical development: one HPV2 vaccine from Walvax (owned by Shanghai Zerun Biotech) and two HPV4 vaccines from Serum Institute of India and China National Biotech Group (CNBG). All use aluminium-containing adjuvants and should be licensed with an indication for girls 9 to 14 years old for both 2- and 3-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.

The base projection foresees a threefold increase in available supply over the mid-term (4–6 years, range 2–5X), from the approximately 60M doses available for 2020, and an approximately fourfold increase in the long term (7–9 years, range 2.5–6X).

NOTE: The SARS-CoV-2 pandemic, including COVID-19 vaccine production, may have an impact on development and production of HPV vaccines. This situation is currently under investigation and requires careful attention.

Supply / Demand Balance

Continuing supply constraints over the past years particularly affected LICs and MICs and led to the calibration of introduction plans and delay of several MACs, especially in the Gavi-supported countries. As a result, for 2020 and up to 2024, the global supply could be sufficient to meet base demand without MACs, in principle (Figure 3). Nevertheless, some countries may still be unable to serve their populations. This can be due to i) country preference for a specific vaccine product, ii) supplier allocation decisions, iii) timing of country plans to catch up on missed vaccination rounds due to the SARS-CoV-2 pandemic, or iv) countries' decisions to conduct MACs.

The implementation of gender-neutral and adult catch-up vaccination policies in additional countries would further exacerbate the constraint. Discussion is ongoing with countries and manufacturers, via the WHO Global Dialogue, to enhance the likelihood that all countries – particularly those with high cases and weak health systems – can introduce before further populations are reached.

Supply/demand balance is expected to finally and steadily improve from 2024, subject to the realization of the following conditions:

- » Current suppliers' sustained commitment to existing programmes, success in expanding capacity and making such capacity available as communicated (both in terms of the timing and size of the increases)
- » Pipeline manufacturers' success in completing their clinical development programmes, obtaining marketing authorisation in the first country, obtaining prequalification, registering their products in all countries where necessary and making supply available in the expected quantities
- » Countries' acceptance for all products irrespective of valency or country of origin
- » Countries' compliance with SAGE recommendations to postpone implementation of MAC campaigns, gender-neutral and older age group vaccination strategies

FIG. 3: SUPPLY / DEMAND BALANCE OVER TIME¹⁷

DEMAND SCENARIOS	BASE SUPPLY			LOW SUPPLY		
	Short-Term (1-3)	Mid-Term (4-6)	Long-Term (6-9)	Short-Term (1-3)	Mid-Term (4-6)	Long-Term (6-9)
Base Case	Red	Yellow	Green	Red	Red	Red
Base Case (No MACs)	Yellow	Green	Green	Red	Red	Yellow
1-dose with MACs	Red	Green	Green	Red	Yellow	Green
Elimination (90% cvge.)	Red	Green	Green	Red	Red	Red

¹⁷ The low supply scenario is based on more conservative assumptions concerning manufacturing capacity increases and success in clinical development.

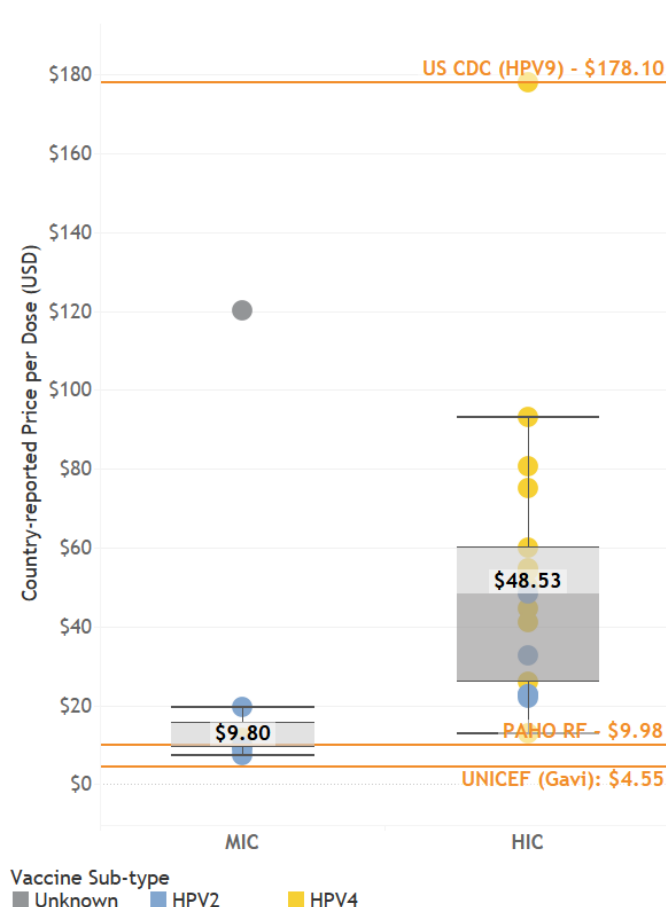
Price

The reported price per dose¹⁸ of HPV vaccines shows a tiered structure by procurement method and income group, with UNICEF Supply Division (SD)/Gavi and PAHO Revolving Fund (RF) paying the lowest prices, at US\$ 4.55 and 9.98,¹⁹ 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. The self-procuring MICs' median prices for both HPV2 and HPV4 are ~2X the Gavi price and similar to the PAHO price.

On average for 2013–2019, GSK's HPV2 product is lower-priced, ranging from US\$ 6.30 to 38.70, compared to Merck's HPV4 product, which ranges from US\$ 8.30 to 113.30 for self-procuring MICs.²⁰ Comparing countries that reported prices in both 2013/14 and 2019, HPV prices have decreased across all procurement and income groups, with self-procuring HICs seeing the largest percentage decrease.²¹ Further significant changes in price are expected to materialize once investments have been recovered and a competitive environment is established.

Affordability remains a concern for MICs that are no longer (or were never) supported by Gavi or PAHO RF. Both Merck and GSK have made price commitments (under specific conditions) to countries transitioning out of Gavi support.²² Some countries are no longer eligible for these time-limited commitments.²³ The overlap between the reported prices paid by MICs and those paid by HICs indicate space for improvement over the current tiered pricing strategies. MI4A conducted an investigation of MICs' ability to pay, product choices for other EPI vaccines, recognition of disease burden, budgetary impact of HPV vaccine introduction, and potential for future external support. This analysis highlighted that affordability of HPV vaccine represents a substantial financial burden for at least eight countries across all regions that have not yet introduced HPV, with a cohort of eligible girls (9 years old) totalling 1.1M. In these countries, the impact of the HPV introduction on health and immunization budgets can represent a significant barrier to introduction that deserves attention and support.

FIG. 4: 2019 HPV SELF-PROCURED PRICE PER DOSE



18 WHO JRF 2019 data.

19 PAHO RF price is the 2018 price, because no HPV price was reported publicly for 2019.

20 Excluding outliers.

21 For self-procuring MICs, there were not enough reported data values in 2019 to compare, but 2018 reported data showed a 3% decrease over 2013/14 reported prices.

22 For details of price commitments, see the fact sheet on vaccine pricing for Gavi-transitioning countries: https://www.who.int/immunization/programmes_systems/procurement/mi4a/platform/module2/Factsheet_vacc_pricing_Gavi_transitioning.pdf

23 Gavi as part of its 5.0 strategy (2021-2025) is outlining parameters for potential engagement with former Gavi-eligible countries and non-Gavi-eligible countries with GNIs per capita of up to US\$ 6,000 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:

- WHO and its partners will assess the impact of the SARS-CoV-2 pandemic on both supply and demand for HPV vaccines to inform short- and medium-term market, policy and programmatic decisions.
- WHO and its partners will continue to convene a Global Access Dialogue engaging all stakeholders to achieve equitable access to scarce supply, including through calibration of demand and supply and implementation of SAGE recommendations.
- WHO will continue to explore opportunities to increase supply flexibility through translating emerging scientific evidence in recommendations on optimized schedules (e.g., 1-dose).
- WHO will continue to inform efforts to increase supply availability and synchronize regulatory efforts, with a particular focus on prequalification of new HPV vaccines.
- WHO will continue to enhance information sharing with countries to inform evidence-based product choices re-affirming the comparable immunogenicity, efficacy and effectiveness of the available quality-assured products.
- WHO and its partners will work with MICs in line with IA2030 and the Gavi 5.0 MICs approach to support introduction of HPV.

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, JSI, and WHO SAGE, along with manufacturers associations (DCVMN and IFPMA) 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 trials information, review of available cost of goods studies, review of manufacturing processes documentation (e.g. EMA), analysis of vaccine products registration.

Demand resources:

Historical procurement: WHO MI4A V3P/JRF (2013–2019) and UNICEF SD (2014–2019). Planned/projected country introductions: WHO JRF, Gavi Operational Forecast, and Global Vaccine Market Model (GVMM) Demand Module. 2019 WHO Estimates on HPV vaccine coverage, 2019 update (IVB Database, July 2020).

Pricing resources:

WHO MI4A V3P/JRF, PAHO RF, UNICEF SD (2019 data).

Other Useful Public Resources

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

UNICEF SD HPV Supply and Demand Update (2020)

<https://www.unicef.org/supply/reports/human-papillomavirus-hpv-vaccine-supply-and-demand-update>

Gavi HPV Roadmap Public Summary (2017)

<https://www.gavi.org/about/market-shaping/supply-and-procurement-roadmaps/>