

GLOBAL MARKET STUDY

HPV

Key Takeaways

- Thirteen years after the first HPV vaccine registration, **53% of WHO Member States have introduced HPV vaccine** into their routine national immunization schedule. Supply constraints to low- and middle-income countries have resulted in a slower introduction pace in those geographies.
- WHO issued a call for action towards **global cervical cancer elimination** in May 2018 which, through national introductions in all countries and increased coverage, is estimated to increase total demand for HPV vaccines to 120M doses or more per year after 2025. Sizeable increases in supply will be required to serve this level of demand.
- **Supply is currently insufficient to meet demand.** According to the MI4A base case scenario, supply constraints are expected **until at least 2023/24**. This situation may change depending on: (a) operational programmes shifting to alternative vaccination strategies, as recently recommended by SAGE;⁶ (b) country acceptance of all available HPV vaccines; (c) the pace of implementation of the investment decisions of current manufacturers; (d) the success, time to registration, prequalification and available supply from the three new manufacturers with programmes in advanced stage of clinical development.
- To address short-/mid-term supply constraints, SAGE recommended that all countries should temporarily **pause implementation of gender-neutral, older age group (>15 years) and multi-age cohort** HPV vaccination strategies as well as consider possible alternative strategies.
- In MICs not supported by Gavi or PAHO Revolving Fund, HPV vaccine can account for up to 56% of a country's total vaccine expenditure. **Affordability is frequently cited by such countries as a barrier** to introduction and to the sustainability of the programme.

6 Meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization, October 2019: conclusions and recommendations, WHO Weekly epidemiological record, 22 November 2019, No 47, 2019, 94 – <https://apps.who.int/iris/bitstream/handle/10665/329962/WER9447-eng-fre.pdf?ua=1> accessed November 26, 2019.

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 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.

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>

QUICK STATS

NUMBER OF VACCINE SUBTYPES¹

3

TOTAL NUMBER OF MANUFACTURERS²

2

2019 ESTIMATED GLOBAL SUPPLY³

~50M doses (maximum)

2019 ESTIMATED GLOBAL DEMAND⁴

~50M doses (supply constrained)

2018 REPORTED PRICE PER DOSE (RANGE)⁵

US \$4.50–\$168.00

Purpose & Background

Several countries across regions and income groups, and in particular Gavi-supported countries, have notified WHO of constraints to their access of HPV vaccines. The issue of affordability has also been raised, particularly by MICs not benefiting from Gavi support. Following the announcement of a call for action towards global elimination of cervical cancer by the WHO Director-General in May 2018, increasing introduction and coverage of HPV vaccine worldwide will be key. This study provides the most updated understanding of current and future global trends and drivers of 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.

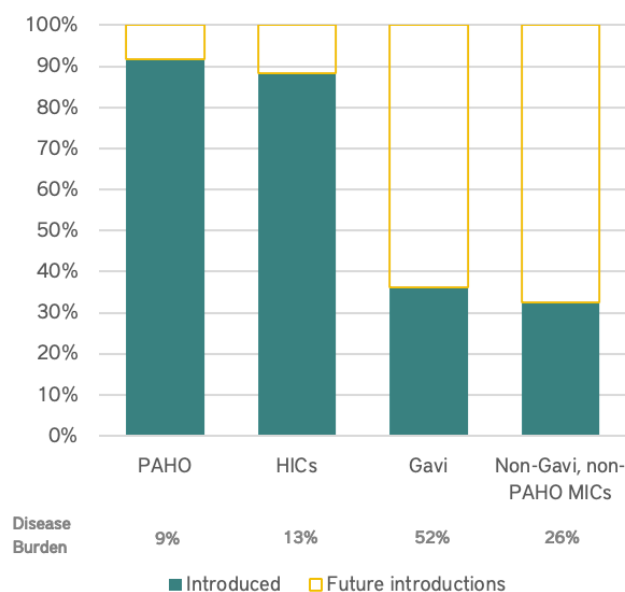
Market Highlights

As of December 2019, 102 countries (53% of WHO Member States, corresponding to 36% of the target population) have introduced HPV into the national routine immunization schedule, with 15 new introductions in 2019. 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.⁷ More than two thirds of the countries (69%)⁸ that have introduced the HPV vaccine are self-procuring. Based on MI4A estimates, approximately 18% of the 2019 global demand is for use in boys.

Currently, three HPV vaccine subtypes are registered: GSK’s Cervarix (HPV2), using the proprietary AS04 adjuvant, and Merck’s Gardasil (HPV4) and Gardasil 9 (HPV9), both using aluminium-containing adjuvant. Merck’s two products are also commercialized by two licensors in the country where they are located (Instituto Butantan in Brazil and Sinergium Biotech in Argentina). Distribution agreements exist in various countries.

Demand in 2019 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 2018 JRF purchase data and MI4A estimates).

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



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”.¹⁰

Global Demand

WHO is estimating programmatic dose requirements¹¹ for all key vaccines in the Essential Medicines List. A global demand forecast for HPV vaccine has been developed for the period 2020–2030 based on the analysis of historical procurement data and the latest available information on country introduction plans, as well as of 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 age¹² and assuming the implementation of a certain number of MAC campaigns.

10 Human papillomavirus vaccines: WHO position paper, May 2017, Weekly epidemiological record, N. 19, 12 May 2017 - <https://apps.who.int/iris/bitstream/handle/10665/255353/WER9219.pdf;jsessionid=922B5115F986B771D2D0AE7E6561B737?sequence=1> accessed November 2019

11 Programmatic doses requirements indicate 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.

12 For HPV vaccines, a 2-dose schedule with a 6-month interval between doses is recommended for individuals receiving the first dose before 15 years of age. Source: Human papillomavirus vaccines: WHO position paper, May 2017, cit.

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

8 Procurement status of countries informed by 2013–2018 JRF purchase data.

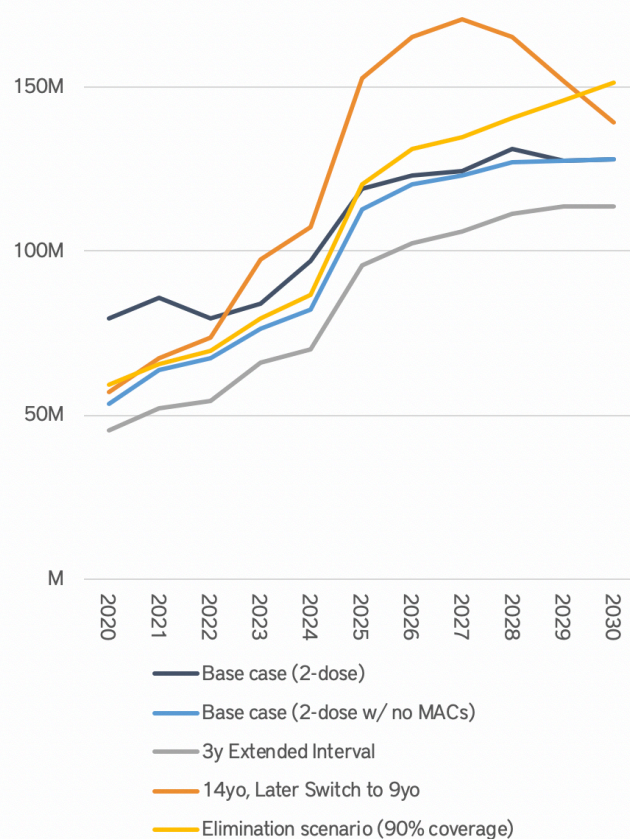
9 Note that 2% of the market share is unknown (due to lack of procurement data from a small number of countries) and is believed to be split between HPV2 and HPV4.

Global HPV programmatic dose requirements remain supply constrained in 2019, totalling ~50M doses, including demand from public and private sectors. Demand not constrained by supply exists in excess of 80M¹³ doses for 2020, reaching ~120M doses in 2025 and stabilizing at that level thereafter. In the short term, increase in demand is largely driven by potential Gavi-supported MAC campaigns;¹⁴ however, given persisting supply constraints, this demand will not be entirely fulfilled. In the mid-term, introductions in China and India national immunization programmes (estimated for 2023 and after) are expected to drive the most significant increases in demand: their combined demand will represent ~one third of the market by 2030. Strong increases in global vaccination coverage due to the global cervical cancer elimination strategy¹⁵ 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 strategies¹⁶ until vaccine supply allows equitable access to HPV vaccine by all countries.”¹⁷ 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.¹⁸

Figure 2 shows the possible evolution of global demand based on various scenarios. The scenario with MAC campaigns has the highest short-term programmatic dose requirement, while a 3-year extended interval results in lowest doses needs in the short-term. Vaccination of 14-year-old girls with later switch to 9-year-olds increases requirements considerably in the mid-term, but eventually, the elimination scenario results in the highest requirements.

FIG. 2: COMPARISON OF BASE CASE DEMAND (WITH YEAR 2020 UNCONSTRAINED), CERVICAL CANCER ELIMINATION, EXTENDED INTERVAL AND 14-YEAR-OLD TO 9-YEAR-OLD SWITCH¹⁹



13 Note that this estimate 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).

14 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.

15 Modeling 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.

16 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 80M doses; estimates of doses requirements from older age group strategy depend on the age group targeted.

17 Ref. WHO Weekly epidemiological record, 22 November 2019, No 47, 2019, 94, p.541–560, cit.

18 Ref. WHO Weekly epidemiological record, 22 November 2019, No 47, 2019, 94, p.541–560, cit.

19 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 “3-year extended interval” scenario models a 1+1 schedule (3-year interval between first and second dose) for all new introductions (2020+) in Gavi-supported and PAHO RF countries. The “14-year – later switch to 9-year” scenario assumes that future introductions in Gavi-supported and PAHO RF countries target 14-year-olds to start, and later, when supply allows, switch to 9-year-olds, maintaining 14-year-olds’ vaccinations until all cohorts are covered. 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. Ref. <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.

The existing manufacturers are currently investing in increased capacity and supply has increased in the past few years; however, the required lead time for those new investments to translate into functioning new production lines will delay the availability of any additional doses to 2022 at the earliest.

Three products are currently in advanced clinical development: two HPV2 vaccines from Inovax and Shanghai Zerun Biotech – the first currently undergoing registration and the second in Phase III – and one HPV4 vaccine from Serum Institute of India, also currently in Phase III. All use aluminium-containing adjuvants and should be licensed with an indication for girls 9 to 14 years old for both 2- and a 3-dose schedules. The success, timing and capacity of these pipeline vaccine efforts will have an important 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 50M doses available for 2019 – and an approximately 4.5-fold increase in the long term (7–9 years, range 3–6.5X).

Supply / Demand Balance

Currently, supply is insufficient to fully meet existing demand.²⁰ As per the supply and demand base case scenarios, this imbalance is forecasted to remain for the short-/mid-term up to 2023/24, especially for LICs and MICs, due to the increased number of countries planning introductions and wishing to conduct MAC campaigns. The inability to serve this growing demand is estimated to be the cause of delayed planned introductions or delayed implementation of planned MAC campaigns in the period 2020–2023 in up to 29 countries.²¹ Scenarios with no MACs/catch-up minimize the impact of supply constraints (further improved with an extended interval schedule) and could allow additional country introductions (see Figure 3).

Implementing commercially attractive gender-neutral and adult catch-up vaccination policies in additional countries, not following the recent SAGE recommendation, would further exacerbate the constraint.

Supply/demand balance is expected to improve in the mid-term, from 2023/24, subject to the realization of the following conditions:

- » Current suppliers’ sustained commitment to existing programs, 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 and in registering their products and obtaining prequalification in time, as well as making supply available as communicated
- » Country acceptance for all products irrespective of valency or country of origin
- » Country compliance with SAGE recommendations to postpone implementation of MAC campaigns, gender-neutral and older age group vaccination strategies

FIG. 3: SUPPLY / DEMAND BALANCE OVER TIME²²

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	Green	Green	Red	Red	Red
Base Case No MACs	Yellow	Green	Green	Red	Red	Yellow
3y Extended Interval	Yellow	Green	Green	Yellow	Yellow	Yellow
14yo Later 9yo	Red	Green	Green	Red	Red	Red
Elimination (90% covg.)	Red	Green	Green	Red	Red	Red

20 To account for stock dynamics in countries, this analysis considers supply as sufficient – even if still tight – when it exceeds demand by at least 10%.

21 Depending on the scenario.

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

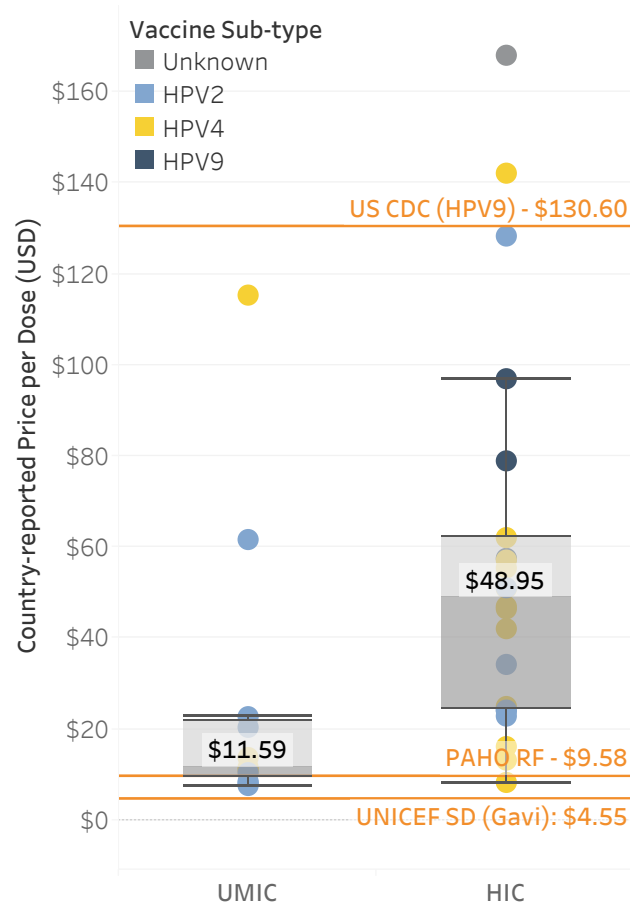
Price

Between 2017 and 2018, the price per dose of HPV vaccine products generally remained stable or decreased slightly. Reported price per dose²³ 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 median prices, at \$4.55 and \$9.58, respectively. The self-procuring MICs' median prices for both HPV2 and HPV4 are ~3X the Gavi price and ~1.5X the PAHO price.

Both Merck and GSK have made price commitments (under specific conditions) to countries transitioning out of Gavi support.²⁴ Some countries are no longer eligible for these time-limited commitments.

An overlap between the reported prices paid by MICs and those paid by HICs indicate space for improvement to the current tiered pricing strategies. Affordability remains a concern for MICs no longer (or never) supported by Gavi or PAHO RF. An analysis of MICs' ability to pay, product choices for other EPI vaccines, recognition of disease burden and budgetary impact of HPV vaccine introduction, and potential for future external support was performed. This analysis of countries that have not yet introduced HPV vaccine highlighted how affordability issues may be a real concern for at least eight countries (across all regions), where a cohort of eligible girls (9 years old) totals 1.1M. In those countries, the impact of the HPV introduction on health and immunization budgets can represent a significant barrier deserving attention and support.

FIG. 4: 2018 HPV SELF-PROCURED PRICE PER DOSE



23 Source: WHO JRF 2018 data.

24 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

Areas for Action

Careful coordination and investments are required to enhance supply availability towards global cervical cancer elimination goals:

- WHO will continue to share its understanding of global supply and demand to inform immunization strategies and the design of the global cervical cancer elimination strategy.
- WHO and its partners will convene a dialogue on global access to HPV vaccine, engaging all stakeholders, to enhance more equitable access to scarce supply, including through implementation of SAGE recommendations.
- WHO will continue to explore opportunities to increase supply flexibility through application of available scientific evidence and recommendations.
- 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 i) product choices with available scientific evidence and ii) operational programmes shifting to alternative vaccination strategies per SAGE recommendations.
- WHO and its partners will work with MICs not supported by Gavi or PAHO RF where affordability is perceived as a significant barrier to introduction and explore alternative modalities for access.

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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 (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, CHAI 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 (COGs) studies, review of manufacturing processes documentation (e.g. EMA), analysis of vaccine products registration.

Demand resources:

Historical procurement: WHO MI4A V3P/JRF (2013–2018) and UNICEF SD (2014–2018). Planned/projected country introductions: WHO JRF, Gavi Operational Forecast, and Global Vaccine Market Model (GVMM) Demand Module. Regional historical coverage: Brotherton & Bloem, 2017 and Bruni, et al., 2016, 2018 WHO Estimates on HPV vaccine coverage (IVB Database, July 2019).

Pricing resources:

WHO MI4A V3P/JRF, PAHO RF, UNICEF SD (2018 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 (2018)

https://www.unicef.org/supply/index_82529.html

Gavi HPV Roadmap Public Summary (2017)

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