

GLOBAL MARKET STUDY

HPV

Key Takeaways

- Twelve years after the first HPV vaccine registration, less than half of WHO Member States have introduced HPV vaccine into the routine national immunization schedule. Introductions are lowest in Gavi 73 countries and non-Gavi, non-PAHO middle-income countries (MICs)
- Supply is currently insufficient to meet demand and some countries have or will have to postpone introductions
- 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 by at least 100M doses over the next 10 years
- To meet the expected increase in demand due to the cervical cancer elimination initiative, sizeable increases in supply will be required. Constraints are expected until at least 2024, assuming the base case supply scenario. This timing may change depending on selected vaccination strategies and investment decisions of current manufacturers, as well as on the timing of the three programs in advanced stage of clinical development
- Meeting the projected demand volumes required for multi-age cohort (MAC) introductions (9–14 years of age), as per WHO recommendation, will remain especially problematic in large countries, as well as meeting additional demand generated by implementing gender-neutral HPV vaccination
- Affordability of HPV vaccines in non-Gavi MICs is a barrier which needs to be addressed to encourage introduction

QUICK STATS

NUMBER OF VACCINE SUBTYPES¹

3

TOTAL NUMBER OF MANUFACTURERS²

2

2018 ESTIMATED GLOBAL SUPPLY

~30 million doses (maximum)

2018 ESTIMATED GLOBAL DEMAND

~30 million doses (supply constrained)

2017 REPORTED PRICE PER DOSE (RANGE)

US \$4.50–\$154.28

Purpose & Background

Several countries across regions and income groups have notified WHO of constraints to their access of HPV vaccines. The issue of affordability has also been raised, particularly by non-Gavi MICs. 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. Working to understand current and future global trends and drivers of supply and demand, this study aims to address the current and expected constraints and to serve as an important resource for the development of the cervical cancer elimination strategy.

Market Highlights

As of May 2018, 81 countries (42% of UN Member States, corresponding to 25% of target population) had introduced HPV into the national routine immunization schedule.³ Despite carrying the greatest share of disease burden⁴, LICs and MICs are lagging in the introduction of HPV vaccine. To date, the majority of the countries have self-procured HPV vaccines (74% in 2017).

Currently, three HPV vaccine sub-types are available on the market: GSK's Cervarix (HPV2), using the proprietary AS04 adjuvant, and Merck's Gardasil (HPV4) and Gardasil 9 (HPV9), both using alum adjuvant. Merck's two products are also commercialized by two licensors (Instituto Butantan in Brazil and Sinergium Biotech in Argentina). Distribution agreements exist

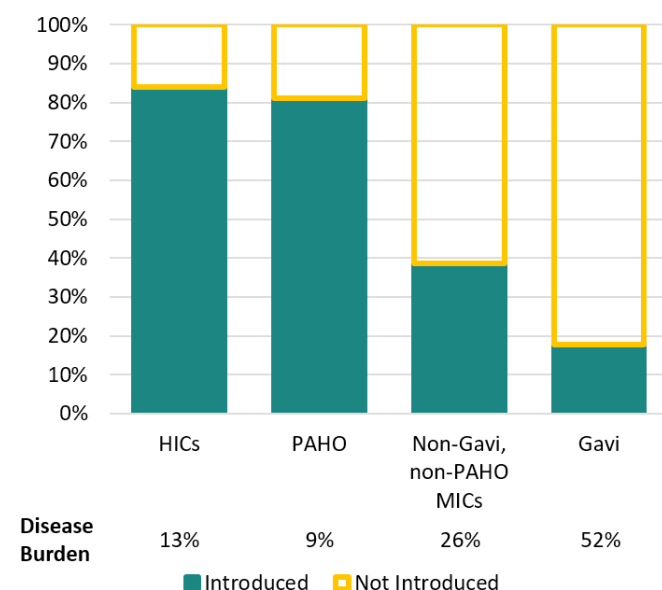
¹ Vaccine Subtypes differentiate by the antigen content of the various HPV vaccines, in this case there are three distinct vaccine sub-types available on the market: HPV2 (16,18), HPV4 (6,11,16,18) and HPV9 (6,11,16,18,31,33,45,52,58)

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 WHO/IVB Database, as of 15 May 2018

⁴ HPV cases (all cancers), women. Source: IARC, Globocan data, 2012

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



in various countries. Current available evidence suggests that the three licensed HPV vaccines have relatively similar effectiveness in preventing cervical cancer.⁵

Estimated market share (volume) are as follows: HPV4: 52%, HPV9: 25% (increasing by 7% over 2016), HPV2: 21%.⁶ Though HPV vaccines make up only ~1% of the global vaccine market by volume, they account for ~15% of global market value (per 2017 MIAA estimates).

Global Demand

Based on the analysis of historical procurement data (2013–2017) and country introduction plans, as well as of key drivers of demand, a global demand forecast for HPV vaccine has been developed for the period 2018–2030. Base demand is estimated to be 55M doses in 2019, reaching ~100M doses in 2025 and stabilizing at ~110M annual doses from 2028 onward. Increased demand in 2019 and 2020 is driven largely by planned Gavi-supported MAC campaigns.⁷ Future projected introductions in China and India (estimated for 2021+) will drive the most significant increases in demand, representing ~1/3 of the market by 2030.

This report evaluated demand scenarios (see Figure 2) around the potential impact for 2019–2030 of a cervical cancer elimination strategy⁸ (additional ~100–250M doses depending on strategy⁹ chosen), a possible 1-dose schedule recommendation¹⁰ (a decrease of up to 250M doses), and potential for more countries to adopt a gender-neutral immunization policy (an additional 135M doses). Rapid implementation of MAC campaigns or increased country adoption of gender-neutral immunization policies will result in the

greatest increase in future demand.

Global Supply

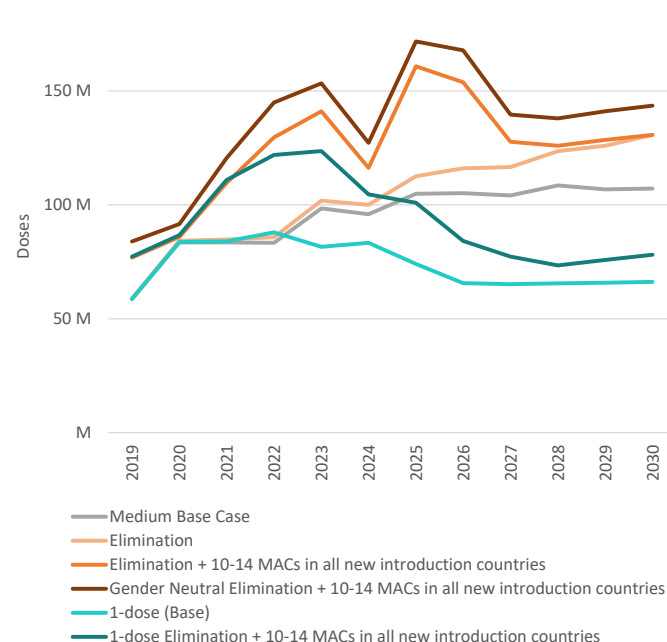
Consultations with manufacturers and experts, as well as a review of publicly available information on HPV vaccines, provides the basis for an assessment of the current and future global supply of HPV vaccine.

Increases in capacity are currently under consideration by the existing manufacturers; however, the required lead time will delay the availability of additional doses to the beginning of the next decade. At the same time, any increase in allocation of manufacturing capacity to HPV9 (versus HPV4) will result in decreases in total output, given the higher requirements to produce a nonavalent vaccine compared to a quadrivalent one.

Three products are currently in advanced clinical development: two HPV2 vaccines from Inovax and Shanghai Zerun Biotech, both in Phase III, and one HPV4 vaccine from Serum Institute of India currently entering Phase II. All use alum-based adjuvants. The success, timing and capacity of these pipeline vaccine efforts will have an important impact on the health of the HPV vaccine market.

The base projection foresees a threefold increase in available supply

FIG. 2: COMPARISON OF BASE CASE DEMAND AND SCENARIOS



⁵ WHO HPV Position Paper, May 2017

⁶ 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

⁷ 48 Gavi-supported countries are forecasted to conduct MACs in the next 10 years – only planned Gavi MACs are included in the base demand forecast

⁸ HPV vaccine introductions across the globe with all countries reaching at least 80% coverage by 2030

⁹ Two elimination strategies were modeled: 1. No additional MACs and 2. MACs for five age cohort in all new introduction countries (2018–2030)

¹⁰ Studies are ongoing to assess the level of protection provided by the administration of a single dose of the HPV vaccines. Preliminary results are expected by 2021/2022

over five years (range 2–6X) – from the approximately 30M doses available for 2018 – and a more than fivefold increase over 10 years.

Demand-Supply Balance

Currently, supply is insufficient to fully meet existing demand.¹¹ This imbalance is forecasted to grow and remain problematic for the short/mid-term due to an increased number of countries planning introductions, including MAC campaigns. Only from 2024 onward is supply expected to support demand (with tight management and careful planning) as per the base case demand and supply scenarios. However, routine demand alone, excluding all MAC campaigns, can be supported starting from 2020 with careful management of country introductions.

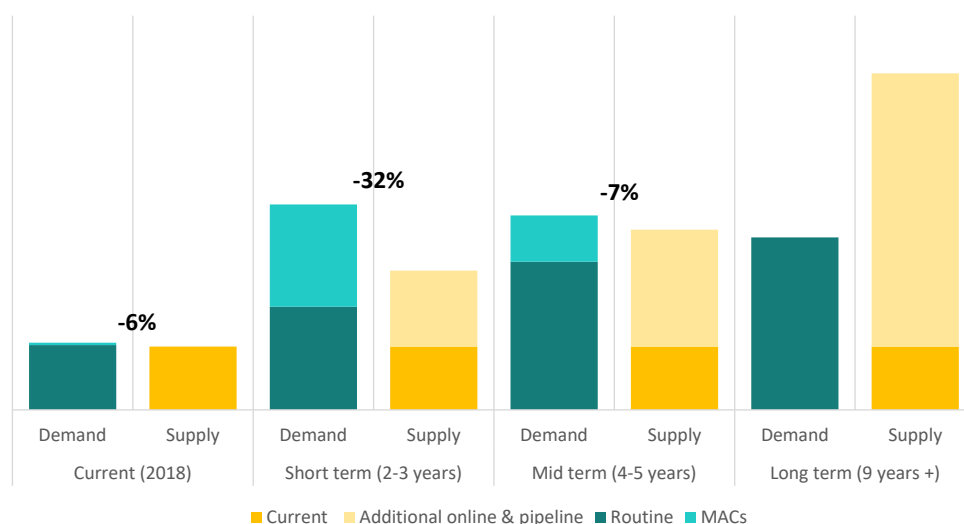
Aggressive capacity increases and faster product development in the context of the call for action to cervical cancer elimination could lead to a sufficient supply to support demand – inclusive of five age cohort

MAC campaigns from 2022. Immunization partners are in active discussions with manufacturers to expedite all activities that can improve the supply situation.

Several risk factors may alter the forecasted balance:

- Timely materialization and size of production capacity increases
- Time to market and size of available supply of pipeline products (domestic and global)¹²
- Use of HPV9 and impact on total supply availability
- Extension of immunization to boys
- Evidence on the level of protection from a single dose of HPV vaccine
- Implementation of MACs by countries and selected target age groups
- Timelines of country introductions and uptake speed

FIG. 3: DEMAND-SUPPLY BALANCE OVER TIME¹³



Price

Reported price per dose¹⁴ of HPV vaccines is tiered by procurement method and income group, with Gavi (UNICEF Supply Division [SD]) and PAHO Revolving Fund (RF) paying the lowest median prices, at \$4.55 and \$9.15, respectively. The non-Gavi MIC (UNICEF- and self-procuring) median prices for both HPV2 and HPV4 are ~3X the Gavi price while HICs pay ~7X the Gavi price. Between 2016 and 2017, the

price per dose of HPV vaccine products generally remained stable or decreased slightly.

Both Merck and GSK have made price commitments to countries transitioning out of Gavi support; nevertheless approximately five of these countries are no longer eligible for these commitments.¹⁵ Affordability remains a concern for non-Gavi MICs, some of which reported paying higher prices than HICs (see Figure 4).

¹¹ 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%

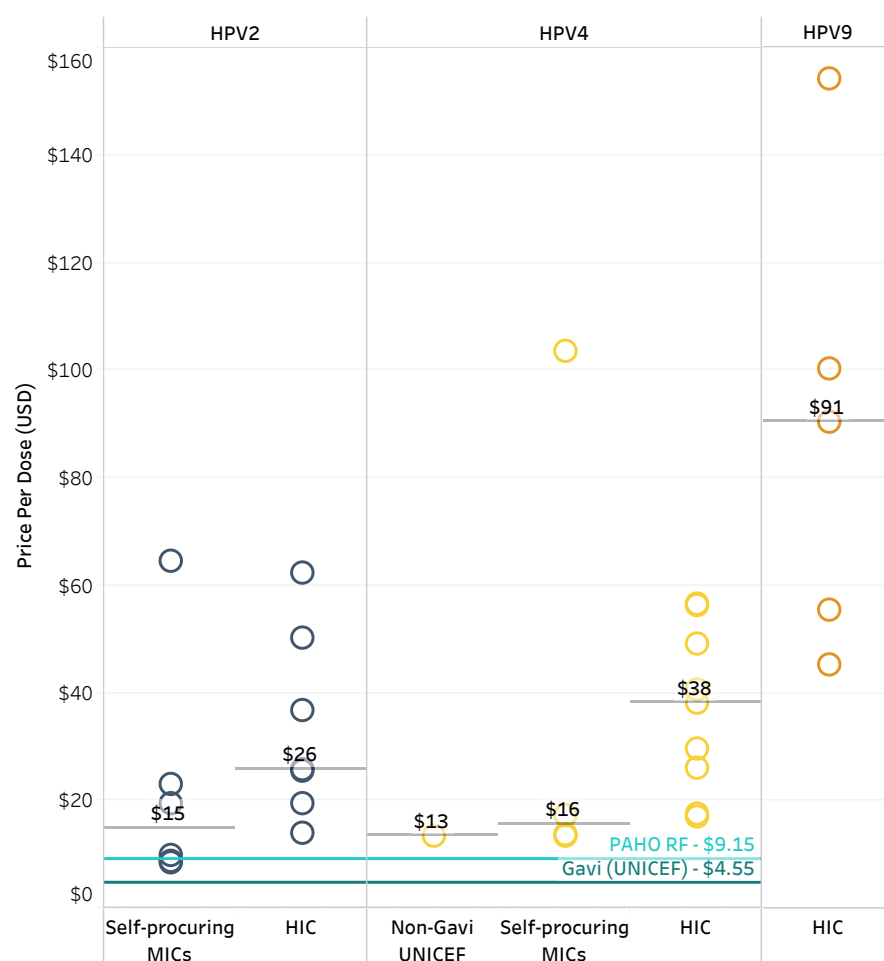
¹² Regulatory aspects should be taken into account

¹³ Base case – Brazil, Argentina, China, and India excluded

¹⁴ Source: WHO JRF 2018 data

¹⁵ For details of price commitments, see MI4A factsheet on vaccine pricing for Gavi-transitioning countries: http://www.who.int/immunization/programmes_systems/procurement/v3p/platform/module2/en/

FIG. 4: 2017 PRICE PER DOSE FOR HPV, BY PRODUCT



Methodology & Data 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.

Demand Resources: Historical procurement: WHO MI4A V3P/JRF (2013–2017) and UNICEF SD (2014–2017). 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.

Supply Resources: MI4A annual data collection from manufacturers, high-level validation of output of analysis with studies from Gavi, CHAI and BMGF, bilateral discussions with manufacturers on capacity drivers and pricing prospects, review of clinical trials information, review of Cost of Goods (COGs) available studies, review of manufacturing processes documentation (e.g. EMA), analysis of vaccine products registration.

Pricing: WHO MI4A V3P/JRF (2017 data)

Areas for Action

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

1. WHO will continue to share its understanding of global supply and demand to inform immunization strategies and the design of the Cervical Cancer Elimination Strategy as well as enhance dialogue on global needs across HPV vaccine market segments to improve supply allocation
2. WHO will explore opportunities to increase supply flexibility through application of available scientific evidence
3. WHO will inform continued efforts to increase supply availability and synchronize regulatory efforts
4. In particular, WHO will enhance information sharing with countries to inform product choices with available scientific evidence and explore opportunities for clearer understanding of country product preferences
5. WHO aims to identify non-Gavi, non-PAHO MICs where affordability is the major barrier to introduction and explore opportunities for improvements

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/files/HPV_2_Status_Update.pdf
- Gavi HPV Roadmap Public Summary (2017): <https://www.gavi.org/about/market-shaping/supply-and-procurement-roadmaps/>

For more information, contact:
vaccinesupply@who.int