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Human Papillomavirus Vaccine: Supply and Demand Update

UNICEF Supply Division

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Human Papillomavirus Vaccine Supply & Demand Update – June 2018

This update provides information on human papillomavirus vaccine, including supply, demand, and pricing trends. It highlights pricing concerns of self-funding middle-income countries, as well as increased demand against constrained supply over the period 2018-2019 following changes in Gavi's programme design.

1. Summary

- Total UNICEF human papillomavirus (HPV) vaccine procurement over 2013-2017 reached 12.9 million doses. UNICEF procured 10.8 million doses (84%) for countries supported by Gavi, the Vaccine Alliance (Gavi), and 2.04 million doses (16%) for self-financing middle-income countries (MICs).
- Gavi has supported HPV vaccine introduction since 2012. Early demand projections for Gavi-supported countries indicated HPV vaccine demand could reach 63.2 million doses over 2013-2017. However, the demand did not materialize as projected: The World Health Organization (WHO) recommended a reduction in dose regimen, and many countries delayed full scale HPV vaccine introduction on account of the programme's design, other competing health priorities, as well as having concerns over pricing and affordability. Consequently, HPV vaccine manufacturers reduced production and supply availability to a lower materialized demand.
- In December 2016, Gavi revised its programme approach to support full-scale national HPV vaccine introduction, with multi-age cohort vaccinations. This substantially increased HPV vaccine demand through UNICEF in 2017, and by January 2018, Gavi had approved an additional 14 countries having applied to introduce HPV vaccines. It anticipates additional country applications during the year, and UNICEF's strategic plan for 2018-2021 seeks to ensure that at least 24 countries have nationally introduced HPV.¹
- HPV vaccine supply through UNICEF is currently not sufficient to meet the increased needs, which it projects could reach 50 million doses in 2019. UNICEF encourages manufacturers to rapidly scale-up HPV vaccine production, as constrained supply through 2019 will affect supply availability for both Gavi country and self-funding MIC demand through UNICEF.
- HPV pricing remains high, and varies significantly between different country income levels. Vaccine affordability is a concern for most self-funding MICs considering HPV introduction, as well as for many Gavi-supported countries seeking to sustain HPV coverage once they transition from Gavi support and self-fund their HPV procurement.
- UNICEF had awarded two suppliers five-year long-term arrangements (LTA) to supply countries supported by Gavi over the 2013-2017 tender period, and recently extended both LTAs through 2018. UNICEF is currently engaged with suppliers to further secure supply for 2019 and beyond.

2. General Brief and Background

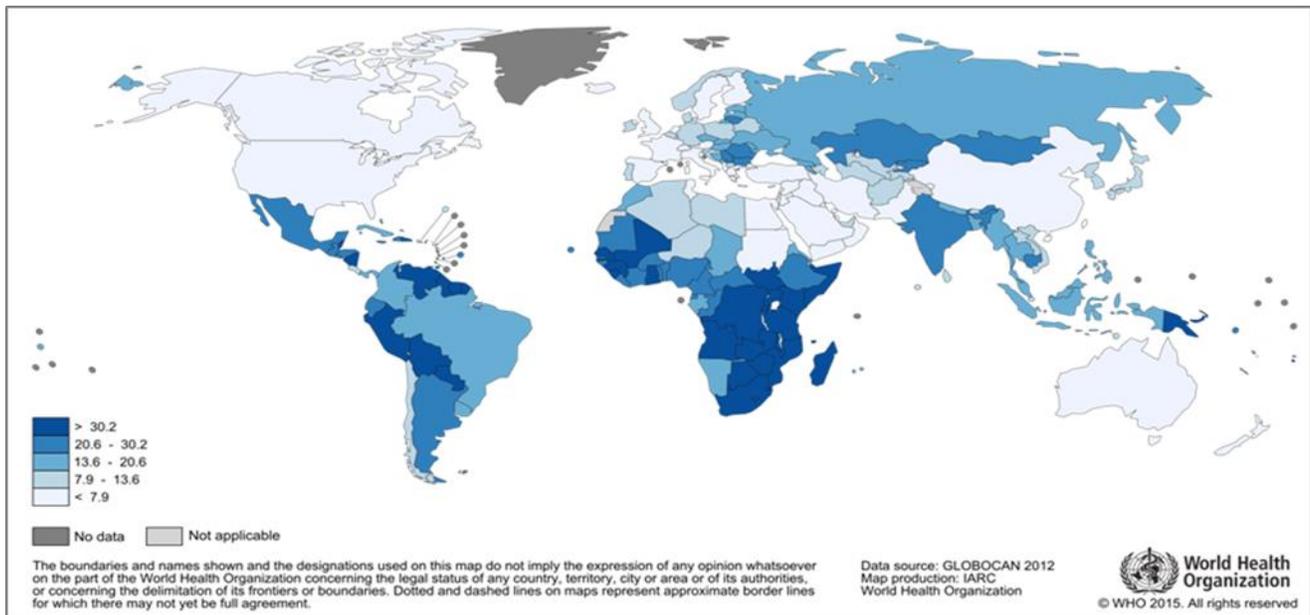
HPV is a group of more than 100 viruses, of which 13 can cause cancer. Nearly all cases of cervical cancer are attributed to HPV.² Globally, cervical cancer is the second most common form

¹ United Nations, [Final Results Framework of the UNICEF Strategic Plan, 2018-2021](#), UN, New York, July 2017, p.19.

² World Health Organization, [Human Papillomavirus and Cervical Cancer](#), WHO, Geneva, June 2016.

of cancer in women,³ with an estimated 530,000 new cases a year, resulting in an estimated 266,000 deaths.⁴ Eighty-five percent of cervical cancer cases occur in less developed regions, with sub-Saharan Africa and Latin America and the Caribbean accounting for the highest incidence rates. Globally, two HPV strains (HPV-16 and HPV-18) cause about 71% of all cases of invasive cervical cancer (Figure 1).⁵

Figure 1 WHO Estimated Cervical Cancer Incidence Worldwide - 2012



Source: World Health Organization

The HPV vaccine is the first vaccine developed specifically targeting the prevention of cervical cancer. HPV vaccines do not prevent all forms of cervical cancer, and as such, it does not replace the need for cervical cancer screening. WHO recommends countries to include HPV vaccination into national immunization programmes as part of a coordinated and comprehensive strategy that includes education, access to quality screening, and treatment. Immunization should primarily target girls aged 9 to 14 years of age, prior to becoming sexually active; and secondarily, to target girls aged 15 and above.⁶ WHO recommends a two-dose schedule for girls aged 9 to 14 years, and a three-dose schedule for girls 15 years of age and above, in accordance with manufacturer guidance.⁷

PATH, an international, nonprofit global health organization focusing on product, service, and system innovation, is coordinating a consortium of nine research institutions that are undertaking the evaluation of evidence for a possible single-dose HPV vaccination schedule. The Single-Dose HPV Vaccine Evaluation Consortium, funded by the Bill and Melinda Gates Foundation (BMGF),

³ Ibid.

⁴ International Agency for Research on Cancer, [Cervical Cancer Estimated Incidence, Mortality and Prevalence Worldwide in 2012](#), IARC, Lyon, December 2013.

⁵ World Health Organization, [Human Papillomavirus Vaccines, WHO Position Paper](#), WHO, Geneva, May 2017, p.244.

⁶ Ibid., p.266.

⁷ Ibid., p.249.

is reviewing the effectiveness of such a single-dose schedule to inform policy discussions, which will impact demand and supply requirements.⁸

WHO has at present prequalified three vaccines from two manufacturers, which all protect against the main strains causing cervical cancer including HPV-16 and HPV-18 (Table 1). Several manufacturers are developing HPV vaccines, including Biotechnology, Inovax, Walvax, and Xiamen in China, as well as Serum Institute of India, amongst others, and which are in advanced clinical trials. More information on HPV vaccines targeting capsid antigens that are either licensed, or in different stages of clinical trials, can be accessed [here](#).⁹ However, UNICEF does not expect any new HPV vaccines to be prequalified by WHO before 2021.

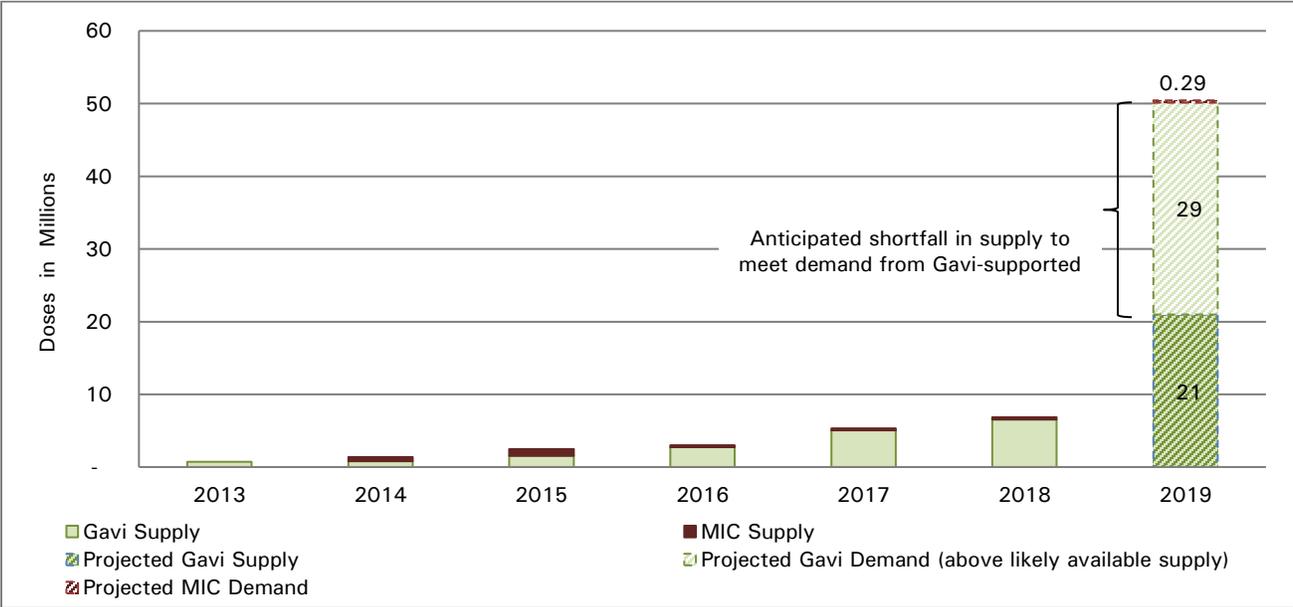
Tabel 1 WHO Prequalified HPV Vaccines

Manufacturer	Type	WHO PQ	Formul	Vial	Shelf Life	VVM	Cold Chain Volume
GlaxoSmithKline (GSK) (Belgium)	Bivalent	2009	Liquid	1 ds	48 months	Type 30	9.7 cm ³
		2009	Liquid	2 ds	36 months	Type 30	4.8 cm ³
Merck (USA)	Tetravalent	2009	Liquid	1 ds	36 months	Type 30	15.0 cm ³
	Nonavalent	2018	Liquid	1 ds	36 months	Type 30	15.1 cm ³

Source: World Health Organization

3. Current Market Situation

Figure 2 UNICEF HPV Supply and Projected Demand 2013-2019



Source: UNICEF Supply Division

From 2010 to 2016, the global market volume for HPV vaccines reached approximately 230 million doses, averaging between 30-35 million doses a year.¹⁰ In 2016, HPV vaccine revenues

⁸ PATH, [New Research Consortium to Evaluate Evidence for Single-dose HPV Vaccination](#), PATH, Seattle, January 2018.
⁹ Roden, Richard, Peter Stern, [Opportunities and Challenges for Human Papillomavirus Vaccination in Cancer](#), Nature Reviews Cancer, London, March 2018.
¹⁰ Gavi, the Vaccine Alliance, [Human Papillomavirus Vaccine Roadmap: Public Summary](#), Gavi, Geneva, December 2017, p. 1.

were estimated at USD 2.5 billion, and are expected to increase to reach an estimated USD 3 billion in 2020, and volumes to reach 75 million doses.¹¹ UNICEF expects the increase in global demand for HPV vaccine will be as a result of increased interest in preventing cervical cancer through immunization, and WHO's global call to action to end cervical cancer, which remains one of the gravest threats to women.¹² UNICEF's strategic plan for 2018-2021 seeks to ensure that at least 24 countries have introduced HPV into their national immunization programme.¹³ There is also the increased tendency for many high-income countries (HICs) to adopt gender neutral vaccination, as well as the recent registration in China of the nonavalent HPV vaccine, all of which may affect supply availability through UNICEF.

By comparison, from 2013 to 2017, UNICEF procured 12.9 million doses of bivalent and tetravalent vaccines for both Gavi-supported countries and self-funding MICs totalling USD 72.6 million.¹⁴ Countries have not yet procured any nonavalent vaccine through UNICEF to date. Based on suppliers' indications on short-term supply availability, UNICEF anticipates to secure a minimum of 21 million doses in 2019, out of a total projected demand that could reach up to 50 million doses, mostly on behalf of Gavi-supported countries (Figure 2).

3.1 Gavi-Country Demand¹⁵

Gavi has supported HPV vaccine introduction since 2012, and initially offered eligible countries two introduction pathways, either through small-scale demonstration projects, or by directly rolling-out national introduction. Gavi had identified 47 countries as eligible to apply for HPV support, and had set a target to vaccinate 30 million girls by 2020, with a demand forecast to reach approximately 63 million doses over the period 2013-2017.

By 2017, total HPV vaccine procurement through UNICEF had only reached 10.8 million doses (Figure 2). In 2014, the forecast demand had been reduced by one third after WHO recommended to reduce the HPV vaccine dose regimen for girls aged 9 to 14 years from three-doses to two-doses. Countries were also taking longer than expected to transition from demonstration projects to national introductions. Even though 23 Gavi-supported countries had conducted HPV vaccine demonstration programmes, only three countries, Honduras, Rwanda, and Uganda, had introduced HPV into their national immunization programmes.

The programme's design delayed national scale-up as demonstration projects did not encourage countries to identify cost-effective, sustainable delivery strategies, and were not integrated into many countries expanded programmes on immunization (EPI). Countries were also hesitant because they perceived programmatic and co-financing costs to be high, and they had pressure from other competing health and vaccine priorities.

To overcome some of these challenges, in December 2016, Gavi redesigned its HPV programme so that national introduction would no longer require prior evidence of experience in delivering HPV vaccines to adolescent girls, and encouraged countries to immunize multi-age cohorts from 9 to 14 years of age in the first year of their programme. As part of the redesign, Gavi also increased its target to vaccinate 40 million girls against HPV by 2020.

As of January 2018, Gavi has approved 14 countries under the redesigned programme to support HPV vaccine introduction, including support for multi-age cohorts in the first year of introduction.

¹¹ Ibid., p. 2.

¹² The International Papillomavirus Society, [WHO Is Calling for Global Action to End Cervical Cancer](#), IPVS, Geneva, May 2018.

¹³ United Nations, [Final Results Framework of the UNICEF Strategic Plan, 2018-2021](#), p.19.

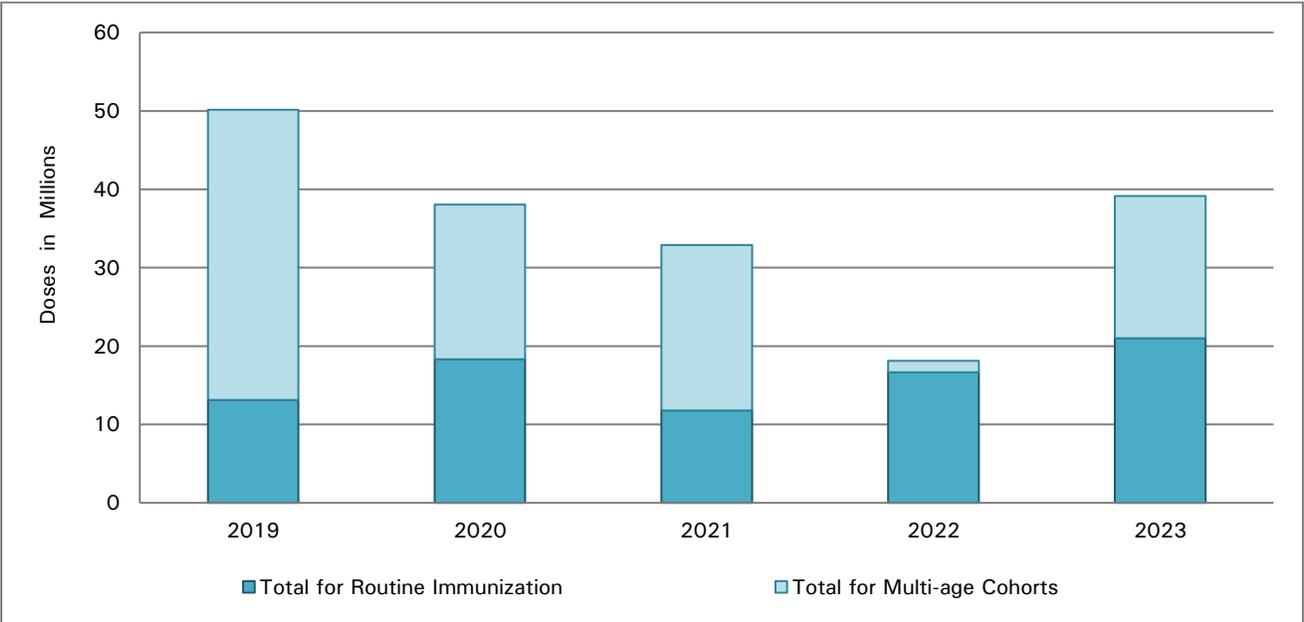
¹⁴ UNICEF, [Price Data Overview](#), UNICEF, Copenhagen, March 2018.

¹⁵ Gavi country demand refers to demand from the Gavi 73 countries.

Due to limited supply availability, manufacturers allocated a limited supply of HPV vaccine to Gavi eligible countries of approximately 7 million doses for 2018. UNICEF anticipates total unconstrained demand could reach up to 50 million doses in 2019 due to multi-age cohort vaccinations combined with additional country applications in 2018 (Figure 3).

However, UNICEF anticipates that beyond 2019, demand through UNICEF will decline to average out at approximately 32 million doses a year over 2020-2023, depending on supply availability to support vaccine introduction and multi-age cohort campaigns. UNICEF expects that once supply availability can meet the increased demand from multi-age cohort campaigns, the requirements for routine immunization through UNICEF could reach approximately 21 million doses a year from 2023 onwards.

Figure 3 UNICEF HPV Projected Demand 2019-2023 for Gavi-supported Countries



Source: UNICEF Supply Division

3.2 Gavi-Country Supply

UNICEF’s last HPV vaccine tender secured supply to support HPV demonstration projects and national introductions with two five-year LTAs through two manufacturers covering 2013-2017. During this period, UNICEF procured 10.8 million doses of HPV vaccine for 36 Gavi-eligible countries. As the demand from countries did not materialize in line with the level originally anticipated, manufacturers curtailed their production capacity through UNICEF to reflect its actual level. The recent increase in HPV vaccine demand during 2017, following Gavi’s HPV vaccine programme redesign, has now surpassed total supply availability from both manufacturers. To meet this demand, manufacturers must substantially scale-up vaccine production capacity and supply through UNICEF in a relatively short space of time.

As current supply through UNICEF is constrained, UNICEF and countries had to review their HPV vaccine introduction plans and multi-age cohorts timing schedules against the timing of manufacturers’ supply availability. UNICEF anticipates manufacturers will need two years to scale-up their production capacity to meet this forecast demand, and as such, supply constraints will likely last through 2019, and possibly into 2020. As UNICEF is not certain as to when manufacturers will have sufficient HPV vaccine supply for countries currently approved by Gavi

for vaccine introductions, UNICEF encourages countries considering to apply to Gavi for HPV vaccine support should do so nevertheless, but to bear in mind that there could be a 15-18-month lead time for vaccine delivery, and so, to plan the introduction timings accordingly.

UNICEF recently extended its current LTAs with both manufacturers by another year through to end-2018, and increased the total number of awarded doses for the period 2013-2018 to 14.3 million (Table 2).

Table 2 UNICEF HPV Vaccine LTA Awards for Gavi-Eligible Countries 2013-2018

Manufacturer (Country)	Type	Price per Dose	LTA Duration	LTA Duration	Total Awards
GSK (Belgium)	Bivalent	USD 4.60	6 years	2013-2018	2,510,660
Merck (USA)	Tetravalent	USD 4.50	6 years	2013-2018	11,822,820
Total					14,333,480

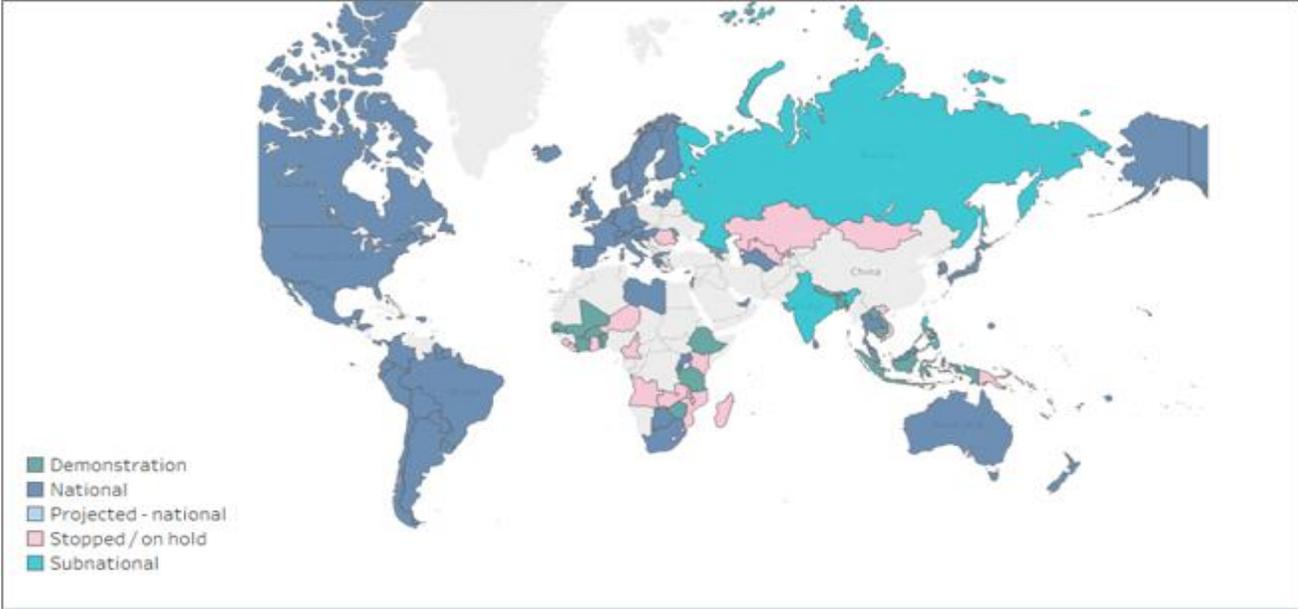
Source: UNICEF Supply Division

Whereas UNICEF had previously made incremental awards to manufacturers during 2013-2016 based on the forecast demand of approved country programmes, in 2017-2018 UNICEF limited awarded quantities in line with manufacturers’ supply availability. UNICEF is currently engaging with suppliers to further secure supply for 2019 and beyond.

3.3 Middle-income Country Demand and Supply

As of April 2018, 99 countries and territories, representing 44% of the global total, have HPV vaccine in their national schedule. Most of these are HICs and upper middle-income countries (UMICs), with many low-income and lower middle-income countries (LICs and LMICs) not yet having introduced the vaccine (Figure 4).

Figure 4 Status of HPV Vaccine Country Introductions Worldwide 2017



Source: PATH

Some MICs that are not eligible for Gavi support, and self-fund HPV vaccines, channel their procurement through UNICEF. Since 2013 through to the end of 2017, UNICEF procured 2.8 million doses on behalf of four countries and territories not supported by Gavi through ad hoc single-country tenders: the Cook Islands (New Zealand), Peru, the Philippines, and Turkmenistan.

Sporadic demand through UNICEF limits the opportunity and ability to develop procurement options to secure sustained and affordable supply. Any incremental supply availability in response to ad hoc demand that materializes outside UNICEF’s annual forecasting exercise will need to be confirmed with suppliers and may be subject to longer lead times for delivery. Lead times for delivery are not based on any country classification, but rather on whether demand was forecasted and planned for. UNICEF recommends all countries to forecast their requirements in advance to ensure UNICEF can secure timely supply from manufacturers, and avoid any delays due to late order placements.

3.4 Pricing

Most countries considering HPV introduction, as well as those seeking to sustain HPV coverage after they transition from Gavi support, and have to self-fund their HPV procurement, are concerned about the high level of HPV vaccine pricing. Whereas both GSK and Merck have committed to continue to provide countries that have transitioned from Gavi support with vaccines at the same prices they accessed when supported by Gavi (Table 2), they also will maintain the HPV vaccine prices these countries are currently paying, within certain timeframes.¹⁶ However, prices offered by manufacturers to MICs that self-fund their HPV vaccine purchases through UNICEF have been significantly higher, and can range from USD 11.64 to USD 31.50. These prices represent between two and half, to seven times the price offered to Gavi-supported countries (Table 3).

Table 3 UNICEF Middle-income Country HPV Vaccine Procurement 2013-2017

Vaccine	Manufacturer	Vaccine Price Range per Dose	Total Award in Doses
HPV	GSK (Belgium)	USD 15.75 - 31.50	2,100
HPV	Merck (USA)	USD 11.64 - 15.00	2,038,940
Total			2,041,040

Source: UNICEF Supply Division

Beyond procuring through UNICEF, Figure 5 highlights the notable variances in prices per dose offered to countries in different income classification tiers, as well as to countries in the same tier, and which is a growing concern for UNICEF and countries.¹⁷

To secure better HPV vaccine prices, UNICEF advises self-funding MICs seeking to procure through UNICEF to forecast and plan their demand and commit to multi-year procurement volumes. Manufacturers may offer better pricing and secure availability if the needs for vaccines are identified, planned, and secured against longer timeline procurement commitments.

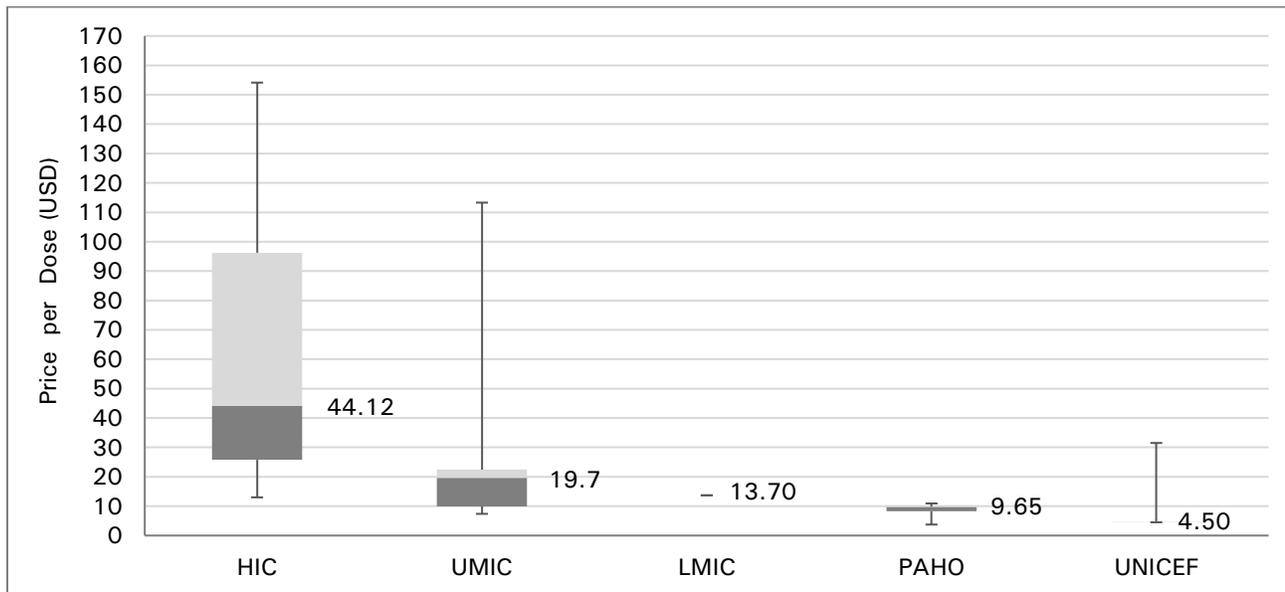
For example, UNICEF has procured ad hoc HPV vaccines on behalf of one self-funding MIC since 2016, and secured 280,000 doses at a cost of USD 15.00 per dose. In order to secure a bigger HPV vaccine price discount, UNICEF re-tendered for HPV vaccines in 2017 on behalf of this country, based on a multi-year commitment by the government to procure HPV vaccines through UNICEF until 2020, for an annual requirement of between 260,000 and 280,000 doses. UNICEF negotiated an LTA with the supplier to supply 1.2 million doses, and a price reduction of 11%, to USD 13.40 per dose. In absence of a critical mass of self-funded MIC demand, based on

¹⁶ Gavi, the Vaccine Alliance, [Vaccine Price Commitments for Countries Transitioning Out of Gavi’s Financial Support](#), Gavi, Geneva, November 2016.

¹⁷ World Health Organization, [Vaccine Product, Price and Procurement \(V3P\) Web Platform](#), WHO, Geneva, March 2018.

country multi-year commitments, UNICEF negotiated tangible, albeit modest, price-reductions with manufacturers for the benefit of the country.

Figure 5 HPV Price per Dose Ranges per Income Group 2016 Showing Median Price¹⁸



Source: World Health Organization, Vaccine Product, Price, and Procurement (V3P) database
 Source: UNICEF Supply Division

3.5 Healthy Market Framework

Figure 6 Application of the Health Market Framework to HPV Vaccine Market



BMGF, Gavi, and UNICEF, developed the Healthy Markets Framework (HMF).¹⁹ HMF is a tool to support market shaping and is used to assess and articulate a market’s current and desired future state. UNICEF and partners use it to identify a set of attributes that measure the health of a particular market; to provide a process to value it specifically for vaccines; and to provide a framework to describe its desired healthy state. BMGF, Gavi, and UNICEF analysed the HPV vaccine market in 2017 (Figure 6).²⁰

Source: Gavi

The HMF showed that it was in a low state of health, and anticipates it will evolve towards a moderate state of health by 2020. The HPV market is rated low in five of the eight attributes:

¹⁸ **Figure 5:** UNICEF uses a “box and whisker” chart to show data distributed per quartile. It highlights price data and ranges in sections each containing approximately 25%. The “box” spans the interquartile range showing 50% of the price data, with the median price marked by a vertical line inside the box separating the two shaded halves, each containing 25% of the data. The “whiskers” show the minimum and maximum price range of the data set. Looked at overall, the chart shows you the spread of a product’s price range per country income classification tiers.

¹⁹ Gavi, the Vaccine Alliance, [Markets Shaping](#), Gavi, Geneva, May 2017.

²⁰ Gavi, the Vaccine Alliance, [Human Papillomavirus Vaccine Roadmap: Public Summary](#), Gavi, Geneva, December 2017, p. 2.

supply meets demand, country preferences, buffer capacity, total systems effectiveness, and long-term competition. It is rated medium in two attributes: individual supplier risk and product innovation, and only high in one attribute: national regulatory authority risk.

As current HPV supply is not sufficient to meet all Gavi's planned country introduction timelines, newly approved introductions are deferred to account for the timing of supply availability. Manufacturers will have little or no buffer capacity through to the end of 2020. Two WHO prequalified manufacturers currently dominate HPV vaccine's market, of which one supplies 87% of UNICEF's procurement. Improved long-term competition and supply will be met with new market entrants.

4. Issues and Challenges

- Short-term supply to support new HPV introductions in Gavi-supported countries is constrained as manufacturers need to scale up production to meet the increase in demand. Based on manufacturers' commitments, UNICEF expects the shortfall in supply to improve by mid- to late-2019 to meet the adjusted country demand for new HPV vaccine introductions supplied through UNICEF.
- One supplier, supplying 87% of UNICEF's supply, currently dominates the HPV vaccine market. UNICEF does not anticipate any new market entrants with WHO prequalified products before 2021.
- The limited visibility on medium- or long-term demand from self-funding MICs through UNICEF disincentivizes manufacturers from offering, planning, and securing, sufficient supply availability at more affordable prices in response to UNICEF tenders.
- Current HPV vaccine pricing levels and variances also remain a significant concern for countries to budget the necessary funding for long-term sustainable financing of HPV programmes.

5. Steps Forward

- UNICEF is working with Gavi, partners, and countries to adjust short- and medium-term plans for routine and multi-age cohort introductions in line with the timing of supply availability communicated by manufacturers.
- UNICEF is working with manufacturers of WHO prequalified products to review their production plans and supply lead times to deliver HPV vaccine for new country introductions, as well as to encourage potential new market entrants and pipeline suppliers to meet future demand at affordable prices.
- UNICEF is currently engaging with suppliers to further secure sufficient supply of HPV vaccines at affordable prices for Gavi-supported countries for 2019 and beyond.
- UNICEF will continue to explore how to secure affordable prices for MICs that self-fund their HPV vaccine purchases, including through multi-year commitments, pooled procurement, special contracting and negotiation with current and pipeline manufacturers.
- UNICEF will continue to assess country demand and identify actions and approaches to improve self-funding MICs forecast accuracy.
- UNICEF is working with manufacturers and countries to increase the price transparency for doses secured on behalf self-funding MICs. UNICEF has since 2011 published its LTA vaccine pricing as part of its Influencing Markets strategy, and broader commitments to information and price transparency, recognizing that the free flow of information and correcting information asymmetry is critical to underpin an efficient market, and which is accessible [here](#).²¹

²¹ UNICEF, [UNICEF Pricing Data](#), UNICEF Copenhagen, May 2018.

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