

Gavi Strategic Goal 4

*Ensure healthy markets for
vaccines and related products*

Market Shaping Roadmap Human Papillomavirus Vaccines

Public Summary, December 2023

Introduction

Context

Human papillomavirus (HPV) is the primary cause of cervical cancer. According to the 2022 update of the World Health Organization (WHO) position paper on HPV vaccines, the disease was the fourth leading cause of cancer and cancer death in women in 2020, with an estimated 604,000 new cases and more than 340,000 deaths. Disease burden is disproportionately distributed, with approximately 90% of the cases in low- and middle-income countries, where health care infrastructure is often sub-optimal.

Gavi, the Vaccine Alliance first opened application windows for the HPV vaccine programme in 2012. By end 2022, 32 countries had introduced HPV vaccine into their national immunisation programmes with Gavi support, reaching more than 16.3 million girls.

Purpose, scope and roadmap timelines

The roadmap is a foundational tool of Gavi's market shaping strategy, with the purpose of articulating a long-term vision and market strategy designed to align market shaping objectives and target outcomes across the Alliance partners; define a set of interventions to reach these objectives and target outcomes; and inform procurement strategies and decisions.

The roadmap focuses on Gavi-supported countries, which consist of the currently Gavi-eligible countries (54 countries plus India); and former and never Gavi-eligible middle-income countries that are now eligible for support under Gavi's Middle-Income Countries (MICs) Approach (46 countries). It takes a long-term view of the market, starting from 2023 through the next ten years. While market projections cover until 2035, proposed interventions focus on the next five years, which are critical for the Alliance's market shaping strategy.

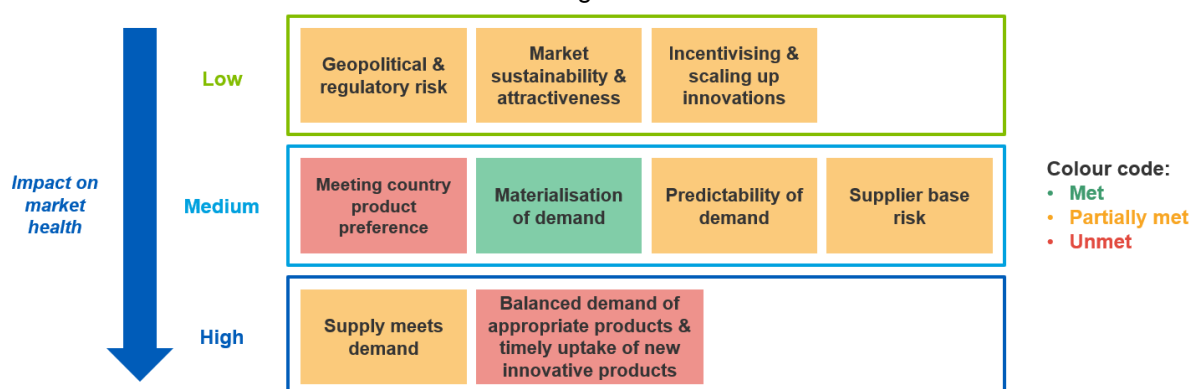
Market health, market shaping vision and strategic objectives

Market health assessment

Gavi's HPV vaccine programme has experienced several major supply-demand imbalances in different phases of the programme's history. The early stage of the programme roll-out (2012–2016) saw limited demand materialisation, resulting in the underuse of available supply; subsequently, manufacturers reduced their supply and capacity for Gavi-supported countries. A redesign of the HPV vaccine programme in 2016 triggered a strong surge in demand for HPV vaccines, which could not be met by the supply available at the time. Increased global interest in response to WHO's call for action towards global cervical cancer elimination and introduction of gender-neutral vaccinations in non-Gavi markets also exacerbated the supply-demand imbalance. In response, the Alliance made a significant market shaping effort, which alongside growing global demand, catalysed capital investment by the incumbent suppliers and product development by pipeline manufacturers. Together with a WHO Strategic Advisory Group of Experts on Immunization (SAGE) permissive recommendation in 2022 of a one-dose schedule, the improved supply has created a market environment that enables implementation of a new strategy to revitalise the HPV vaccine programme. This initiative was approved at the December 2022 Gavi Board meeting, with a target of reaching 86 million girls by the end of 2025.

The 2023–2024 period is considered an inflexion point. While careful supply planning is required in 2023 and 2024, aggregate supply is expected to meet demand in 2025. Beyond 2025, assuming successful entries of new suppliers, aggregate production capacity is expected to become significantly higher than aggregate demand from Gavi implementing countries, including those newly supported by the MICs Approach. This marks a significant improvement in the most critical market health attribute of ‘Supply meets demand’, which was assessed as unmet in all previous years. Figure 1 below indicates an assessment of market health in 2023.

Figure 1



As of December 2023, three WHO-prequalified products are listed on the Gavi product menu: two bivalent (HPV2) vaccines, GSK’s Cervarix and Inovax’s Cecolin; and one quadrivalent (HPV4) vaccine, Merck’s Gardasil. To date, country product preferences are heavily skewed toward the HPV4 vaccine; and product-level supply-demand imbalance continues – meaning two important market attributes are unmet: ‘Balanced demand of appropriate products’ and ‘Meeting country product preference’. Two additional HPV vaccines (HPV2 and HPV4) are expected to be prequalified by WHO in 2024 and 2025. One nonavalent (HPV9) vaccine, Merck’s Gardasil9, is prequalified by WHO and is not yet offered to Gavi-eligible countries. Several manufacturers are developing HPV9 vaccines, some of which would be expected to aim for WHO prequalification.

Figure 2

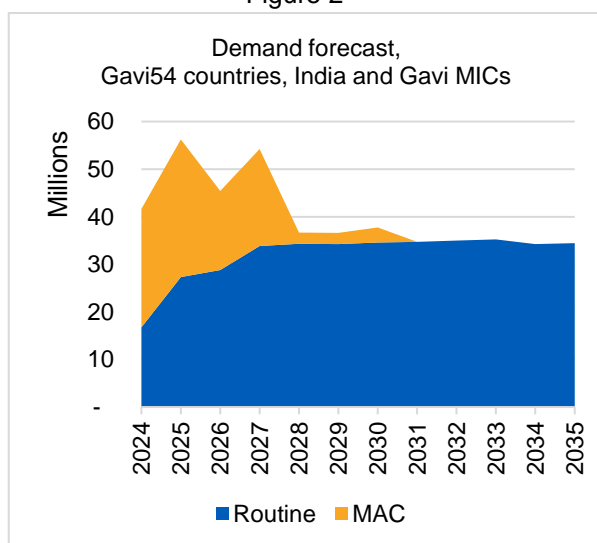
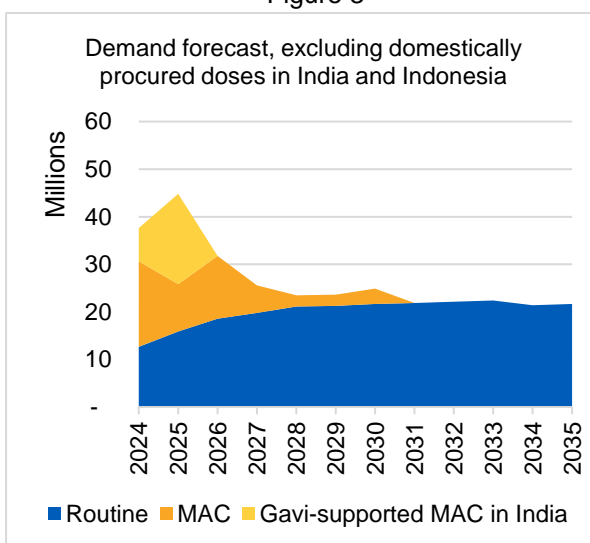


Figure 3



The above figures indicate demand forecasts in doses up to 2035 under the current Gavi HPV vaccine programme design, with a primary target population of girls aged 9–14 years; or through the age of 18 for countries with delayed multi-age cohort (MAC) vaccination which adopt a single-dose schedule. Figure 2 covers all forecasted doses, while Figure 3 excludes doses expected to be domestically procured in India and Indonesia to indicate relevant volumes that could be procured via United Nations procurement agencies.

The projected HPV vaccine demand is characterised by the trend of increasing routine vaccination and the peak of MAC vaccination under the HPV vaccine programme revitalisation, followed by steady routine demand and remaining MAC vaccination. With supply improvement and the programme revitalisation effort, delayed MAC vaccination will be rolled out in large countries, such as Ethiopia and the United Republic of Tanzania; meanwhile, routine introductions with MAC are rolling out in Nigeria and Bangladesh in 2023–2025. India's HPV vaccine launch represents the single largest source of demand.

The forecast assumes that most countries with existing HPV vaccine programmes will shift to a one-dose schedule by the end of 2025; and most countries introducing HPV vaccine into their national immunisation programmes will choose a one-dose schedule.

HPV vaccine market shaping vision and strategic market objectives

The long-term strategy presented in this roadmap aims to ensure an optimal market outcome for HPV vaccines with the following market shaping vision statement:

An HPV vaccine market in which a competitive supplier base produces multiple products that meet varied and evolving country programme needs, supporting sustainable HPV vaccination programmes that in turn foster predictable demand.

The Alliance envisages three market phases, including the current one, leading to a healthy steady state within the next ten years:

- **In the short term (2023–2025)**, additional HPV2 and HPV4 vaccines are expected to enter the market. However, these products will not yet have sufficient evidence during this period to support use of a one-dose schedule. Therefore, product choices will remain practically limited to the incumbent products for countries that have adopted the one-dose schedule.
- **In the medium term (2025/26–2027/28)**, sufficient evidence is expected to support a permissive one-dose recommendation for new entrant vaccines, providing additional and potentially lower-price product options to countries adopting a one-dose schedule.
- **In the long term (2028 and beyond)**, multiple HPV9 vaccines are anticipated to achieve WHO prequalification, creating a competitive environment for HPV9 and providing more product options to countries.

The Alliance aims to have continued access to affordable HPV2 and HPV4 vaccines to ensure sustainability of countries' programmes, while considering cost-effective ways to include higher valency products (such as HPV9 vaccines) on the Gavi product menu to respond to evolving country programme needs. In a situation of healthy competition and sufficient supply from multiple sources, addition of HPV9 vaccines could be adequately timed, subject to a future assessment of HPV9 vaccine offerings against a set of conditions, in order to build on the gains achieved with HPV2 and HPV4 vaccines.

This long-term vision is based on the premise that elimination of cervical cancer as a public health problem is a goal that can be achieved with the use of vaccines containing HPV type 16 and 18 (with the varying levels of cross-protection that they exhibit). The 2022 update of the WHO position paper on HPV vaccines states that from a public health perspective, all currently licensed bivalent, quadrivalent and nonavalent vaccines offer comparable immunogenicity, efficacy and effectiveness for the prevention of cervical precancer and cancer, which is mainly caused by HPV types 16 and 18.

The fundamental consideration is that all countries introduce HPV vaccines (regardless of valency) into their national immunisation programmes, achieving and sustaining high coverage of the primary target population with any of the currently available WHO-prequalified vaccines as guided by the WHO Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem.

With the ongoing and potential challenges and uncertainties across multiple dimensions of the market (supply, demand, policy context), the eventual steady state market is unlikely to emerge without deliberate interventions. Therefore, the Alliance's HPV vaccine market shaping vision translates into the following HPV vaccine strategic market objectives that are aligned with the Gavi 5.0/5.1 strategic period (2021–2025) healthy markets goal:

- **Objective 1** – Supply meets demand to support HPV vaccine programme implementation.
- **Objective 2** – Predictability of medium- to long-term demand is enhanced to facilitate secure supply of affordable vaccines.
- **Objective 3** – Diversity of products suitable for different country contexts is achieved, with healthy competition between suppliers.
- **Objective 4** – Programmatically suitable future innovations are accommodated.

Each objective is underpinned by target outcomes that the Alliance aims to achieve by implementing a set of concerted interventions among Gavi market shaping partners to tackle risks and challenges.

Objective 1 – Supply meets demand to support HPV vaccine programme implementation

TARGET OUTCOMES

1. In the short term, the contracted volume through UNICEF Supply Division (UNICEF SD) is made available and utilised by countries for the optimal implementation of the HPV vaccine programme revitalisation initiative.
2. In the medium to long term, access to affordable HPV2/4 with one-dose data is sustained to ensure countries' programme continuity.

CHALLENGE

While supply improvement in recent years is a positive development, supply-demand imbalances experienced in the Gavi 4.0 period and the complexity of the underlying manufacturing process highlight the importance of close monitoring of timely availability of contracted volume in the coming years. On the other hand, predictability of demand is challenging, since large volumes are tied to MAC vaccination efforts with some unpredictability around when these will be implemented; manufacturers need sufficient time to plan production.

INTERVENTIONS

- Monitor country demand via monthly partner meetings, and keep countries updated on supply lead time to facilitate launch readiness.
- Inform suppliers of the ongoing evolution of operational short-/medium-term demand via frequent touch points with UNICEF SD.

Objective 2 – Predictability of medium- to long-term demand is enhanced to facilitate secure supply of affordable vaccines

TARGET OUTCOMES

3. Clear direction on any future scope of Gavi's HPV vaccine programme (in terms of target population group) is achieved within the medium term.
4. Gavi's MICs Approach in the Gavi 6.0 strategic period (2026–2030) clarifies the future scope and extent of Gavi support to MICs in relation to catalysing and facilitating HPV vaccine introductions and preventing backsliding of coverage.
5. Potential future Gavi funding policies (subject to approval) support meaningful vaccine price sensitivity among Gavi-eligible countries, facilitating healthy supplier competition.
6. Sufficient volume of affordable vaccines is secured to cover projected demand from 2026.

CHALLENGES

The current UNICEF SD contract awards cover the period 2021–2025 with a possibility of an extension of up to two years. There are several post-2025 issues that require more clarity in order to best inform the next procurement strategy and tender:

- The permissive recommendation of a single-dose schedule and countries' adoptions have triggered countries' and suppliers' interest in a potential expansion of the target population to include additional target populations. The current Gavi HPV vaccine programme eligibility covers the WHO-recommended primary target population of girls aged 9–14 years (support available through the age of 18 for countries with delayed MACs that adopt a single-dose schedule), while leaving countries to bear the full procurement cost to reach additional populations.
- In June 2022, the Gavi Board approved a new approach to engaging with middle-income countries with time-limited support until 2025. Under the MICs Approach, Gavi facilitates HPV vaccine introductions in former and never Gavi-eligible MICs. Continuity and design of the MICs Approach are currently under discussion as part of development of the Gavi 6.0 strategy; and will potentially impact the demand and level of procurement through United Nations procurement agencies.
- It is considered that Gavi's co-financing policy affects preferences of initial self-financing countries: with co-financing of US\$ 0.20 per dose regardless of product chosen, initial self-financing countries are not price-sensitive; and they are extremely likely to choose higher valency products by default if such products become available under the current co-financing paradigm.

INTERVENTIONS

- Define Gavi's future programmatic design with regards to additional target population groups.
- Generate more granular MIC demand forecasts for HPV vaccine and define the scope and extent of Gavi support to MICs in the context of Gavi 6.0.
- UNICEF SD to monitor the progress of the interventions for Target Outcomes 3–5 and identify optimal approaches for securing supply through extension of the current contracts and/or optimal timing for upcoming tender periods.

Objective 3 – Diversity of products suitable for different country contexts is achieved, with healthy competition between suppliers

TARGET OUTCOMES

7. Competitive market dynamics and affordable prices are achieved by entry of new suppliers/products.
Sub-targets:
 - a. At least two additional price-competitive HPV2/4 products with one-dose data are available for country adoption in the medium term (2025–2027).
 - b. Multiple price-competitive HPV9 products with one-dose data meet Gavi product menu inclusion conditions for HPV9 vaccines in the long term (2028–2030).
8. Environment for countries' product presentation choice is conducive to evidence-based and price-sensitive decision-making, while maintaining a diversified product portfolio.

CHALLENGES

- While the WHO permissive recommendation is a major facilitator in accelerating countries' roll-out of HPV vaccination programmes, only incumbent products currently have available evidence supporting the one-dose regimen. Given the current product landscape and the time it takes to generate immunobridging data, this situation is expected to continue through the rest of the Gavi 5.0/5.1 strategic period, leaving the newer products unattractive to countries in the one-dose programme environment.
- It is uncertain whether vaccine manufacturers are willing to file evidence with regulators in support of label change for a one-dose schedule, yet off-label use poses challenges to some countries when making vaccine schedule decisions. Exact regulatory requirements for a one-dose schedule label change in relevant national regulatory authorities are yet to be clarified.
- Although HPV9 is currently not available on the Gavi product menu, potential entry of HPV9 vaccines is anticipated in the long run. Careful market phasing is needed in consideration of public health benefits, financial implications and market health, as poorly managed HPV9 entry could have implications for country programme sustainability and could compromise the market attribute of 'Balanced demand of appropriate products'. While the Alliance established a strategic alignment on Gavi product menu inclusion conditions for HPV9 in 2020, it needs to be re-evaluated in the context of current and future market dynamics.
- As the HPV vaccine product portfolio diversifies, considerations for countries' product presentation choices will become more complex. Country choices are affected by the Gavi product menu, the nature of the normative guidance around a one-dose schedule, as well as the individual country contexts (e.g. epidemiology, financial situation). Each element needs to be addressed so that countries are optimally informed while creating an environment for healthy market evolution that will support sustainable programmes in Gavi-supported countries.

INTERVENTIONS

- Continue to advocate and encourage single-dose studies of new entrants' products and publication of evidence for countries' deliberation as early as possible.
- Encourage manufacturers to file for a change to the label to include a one-dose schedule.
- Define conditions under which HPV9 products would become Gavi-financed alongside HPV2 and HPV4, including specific co-financing criteria if necessary, and communicate the defined conditions with suppliers.
- Update the Gavi product menu in the context of new entrants.
- Provide normative guidance when one-dose data for new products becomes available.
- Assess demand for vaccines with different characteristics and country product decision pathways.

Objective 4 – Programmatically suitable future innovations are accommodated

TARGET OUTCOMES

9. Value proposition and use cases of future product innovations are explored/defined.

CHALLENGES

- HPV vaccine microarray patches (MAPs) could in theory bring benefits to the HPV vaccine programme, but the exact value proposition needs clarification. As a programme that is frequently delivered outside of traditional routine immunisation settings (e.g. outreach or school-based delivery), it is conceivable that a MAP presentation could bring benefits to the HPV vaccine programme.
- Several manufacturers are developing higher valency vaccines above and beyond HPV9. However, the public health benefit of these vaccines is not yet understood and could be marginal.

INTERVENTIONS

- Assess and communicate the value of HPV vaccine MAPs to industry and Alliance stakeholders.
- Continue monitoring the vaccine MAPs landscape for progress in HPV vaccine MAPs' development.
- Monitor the progress of the development of higher valency (above HPV9) or 'universal' products.