Gavi Strategic Goal 4

Ensure healthy markets for vaccines and related products

Market Shaping Roadmap
Yellow Fever Vaccines

Public Summary, October 2024

Introduction

Context

Yellow fever (YF) is a mosquito-borne viral haemorrhagic disease, with 34 high-risk countries in Africa and 13 high-risk countries in Central and South America as of 2023. Vaccination is the most important means of prevention, with a single dose of yellow fever vaccine (YFV) sufficient to grant lifelong protection.

YF cannot be eradicated because of the zoonotic reservoir, but epidemics can be eliminated in human populations if immunity levels are raised through mass vaccination and sustained by routine infant immunisation. In view of the proven efficacy and safety of YF vaccination, the World Health Organization (WHO) recommends that all high-risk countries should introduce YFV into their routine immunisation programme (for children aged 9–12 months), in addition to preventive mass vaccination campaigns (PMVCs) for inhabitants aged at least 9 months in areas at risk of YF with low vaccination coverage.

In 2016, a coalition of partners (WHO, UNICEF and Gavi) developed the Eliminate Yellow Fever Epidemics (EYE) Strategy, in response to the increased risk of international spread following two major YF urban outbreaks in Angola and the Democratic Republic of the Congo (DRC). The EYE Strategy aims at ending YF epidemics by 2026 on the basis of 1 billion people protected through vaccination, and it consists of three strategic objectives: (1) protect at-risk populations; (2) prevent international spread; and (3) contain outbreaks rapidly.

The Gavi yellow fever vaccine programme was launched in 2001, among the first vaccines in Gavi's portfolio. With over US$ 1 billion invested since then, Gavi support directly contributes to the EYE Strategy objectives through: (i) an emergency vaccine stockpile for outbreak response, managed by the International Coordinating Group (ICG) on Vaccine Provision; (ii) support for routine immunisation programmes in endemic countries; and (iii) one-time PMVCs for countries at high risk of YF.

Gavi support now also extends to YF diagnostics, with the Gavi's Board's 2018 approval of funding for YF diagnostic capacity strengthening to facilitate more reliable YF laboratory testing, and more effective and efficient YF vaccine usage in outbreak response and in addressing coverage gaps.

Purpose, scope and roadmap timelines

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

The objectives, target outcomes and interventions articulated in the market shaping action plan focus on the currently Gavi-eligible countries and former Gavi-eligible countries, while including global market considerations to highlight interdependencies and their impact on overall market health.

This Yellow Fever Vaccines Market Shaping Roadmap covers a period of ten years (2024–2033), with high-level strategic objectives designed to provide a long-term view.

Market health, market shaping vision and strategic objectives

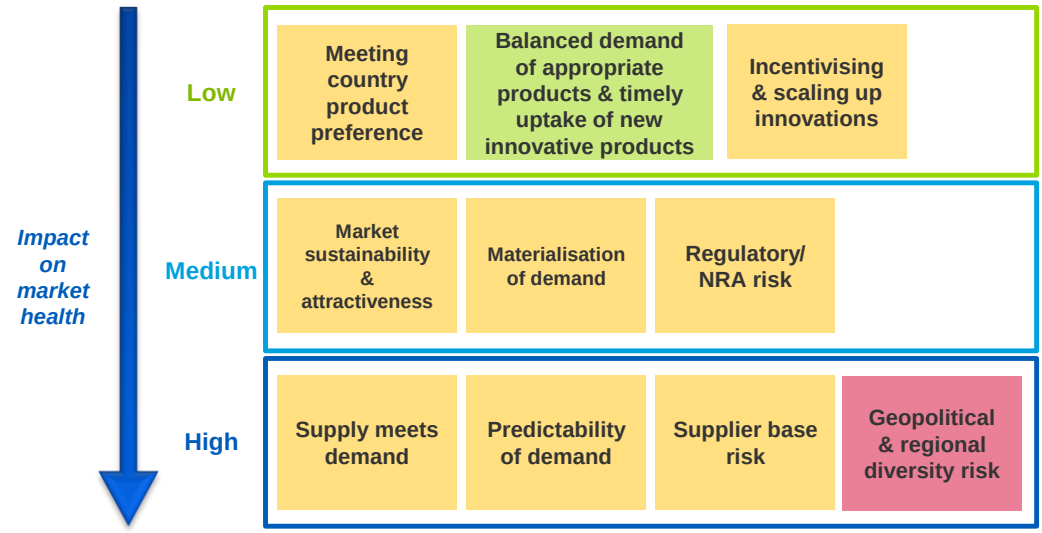
Market health assessment

Global YFV demand emanates from at-risk countries in Africa and Latin America (e.g. Brazil), and from the private/travel market. Historically, demand was heavily constrained by limited supply, which has impacted countries' immunisation plans, causing: rephasing of PMVCs; exceptionally delayed routine introductions; use of fractional dosing; and a prioritisation of stockpile maintenance for outbreak response. Since the last version of this roadmap, dated as of 2017, global demand has increased

significantly due to vaccination campaign activities, in line with the steady ramp-up in supply capacity, resulting in supply meeting total demand with negligible buffer.

The Healthy Market Framework (HMF) assessment shown in Figure 1 (below) is a reflection of YFV market health in 2023, which was rated as 'Acceptable with risks': one attribute was met; eight were partially met; and one was unmet. The YFV market is characterised by a fragile balance of demand and supply, with a continued need to carefully plan large-scale campaigns to optimise allocation of available supply and mitigate against the geopolitical, regulatory and supplier diversity risks associated with Gavi/UNICEF's predominant reliance on two YFV suppliers.

Figure 1: 2023 Healthy Market Framework as assessed for the yellow fever vaccine market



While demand from routine immunisation programmes remains stable, planning and forecasting for the high demand for PMVCs remains a challenge. Activities to improve country planning for campaigns are required and ongoing, to enable a more robust demand forecast and build confidence in timing of demand materialisation.

On the supply side, YFV supply to UNICEF remains highly dependent on two manufacturers (Sanofi Pasteur and Chumakov), despite the existence of four WHO-prequalified vaccines. Chumakov supply has remained reliable to date, but the geopolitical context and recent sanctions experienced by Russia pose an ongoing risk of possible supply disruption, which could have a major impact on YFV market health. Furthermore, while supply capacity has increased significantly in recent years, demand has been rising equally, which explains the persisting fragile supply/demand balance. Investments in production capacity in recent years by several incumbent suppliers are expected to further materialise in the future; however, such additional capacity may quickly become redundant in light of the expected decrease in demand in the long term.

The vaccines' highly desirable characteristics of lifelong protection with a single-dose regimen mean that encouraging innovation has not been a high priority for this market. Product presentation improvements were made in 2022, with the main supplier offering a ten-dose vial presentation and also planning to progressively discontinue the ampoule presentation (which requires more cold chain capacity). The more significant innovation linked to a vero cell candidate vaccine development (with improved process reliability and storage conditions) is not expected to materialise before the end of this decade.

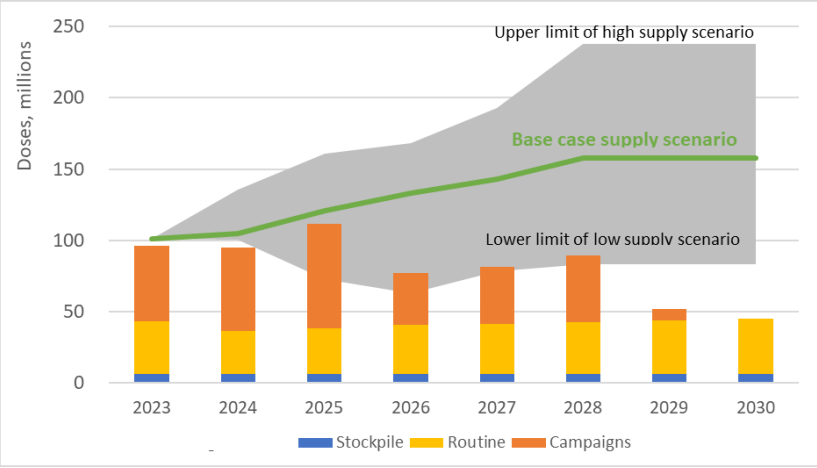
Going forward, the Alliance anticipates three strategic market phases that will guide the roadmap strategy:

Phase 1 (2024–2025): Demand remains high due to PMVCs and planned remaining routine introductions, especially from one large-volume country (Ethiopia). As a result, supply barely meets total demand, which requires continued annual supply prioritisation/allocation led by the EYE partners. Although supply diversification increases with expected output improvements from two of the smaller-scale UNICEF suppliers, supply remains dominated by two manufacturers; and is exposed to the geopolitical risk mentioned above. Uncertainties remain on the timing of Ethiopia's routine introduction and timely implementation of PMVC phases. On the programmatic side, clarity is required from normative agencies with regards to recommendations on the scale and extent of targeted vaccination activities to address coverage gaps. Such guidance is essential to: mitigate the resurgence of yellow fever in countries that are accumulating immunity gaps; sustain the ongoing investments; inform country vaccination plans; ensure relevant resources are secured in a timely manner; and provide manufacturers with sufficient visibility to maintain vaccine production capacity.

Phase 2 (2026–2028): As demand predictability increases with the reduction of PMVC activities, and all routine introductions in high-risk countries are expected to have been completed, the market should reach a good demand/supply balance with a comfortable level of buffer capacity. Excess/buffer capacity is expected to be boosted by the market entry of one pipeline candidate vaccine and by the further supply capacity ramp-up of two of the smaller-scale UNICEF suppliers. This assessment is, however, subject to: clarified guidance on targeted vaccination activities and potentially resulting increased country demand; material epidemiological events and changes in outbreak trends (especially if efforts to reduce immunity gaps are insufficient to mitigate the risk of amplification of yellow fever transmission); and suppliers' commitment to remain in the market based on programmatic updates and the shape of longer-term demand.

Phase 3 (2029–2033): This period is characterised by the end of PMVCs and the stabilisation of demand to routine levels, pending clarity on the scale and extent of targeted vaccination activities. Assuming the market maintains five suppliers at the beginning of this period, excess supply capacity will be significant and likely result in market exits, needing careful management to accommodate any sudden changes on the demand side. Figure 2 (below) overlays the range of supply capacity scenarios (for the UNICEF market) and base case demand scenario for 73 Gavi-supported countries, illustrating the growing buffer capacity, which may be too large to be sustainable as demand declines. Another key factor that may impact longer-term epidemiology and, therefore, potential demand is climate change – since zoonotic transmission in the wild will continue to pose a risk and could be further exacerbated by the expansion of the geographical areas where the vector is present alongside increased human activity in forest areas. Should certain suppliers discontinue production of YFV, the market may become less agile in responding to sudden increases in demand – linked, for example, to a resurgence of outbreaks (which could lead to a renewed risk of supply shortages).

Figure 2: YFV demand/supply comparison (UNICEF market)



YFV vaccine market shaping vision and strategic market objectives

The Alliance YFV market shaping strategy translates into the following three strategic objectives:

- **Objective 1**: Improve predictability of demand to optimise supply use in the short term and increase certainty of demand requirements in the long term.
- **Objective 2**: Achieve a supplier base which in the medium term minimises country plan disruptions due to any manufacturer supply adjustments, and over the long term is diverse and sustainable.
- **Objective 3**: Preferred product characteristics remain available in a context of longer-term demand variations, contributing to increasing coverage and minimised wastage.

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 – Improve predictability of demand to optimise supply use in the short term and increase certainty of demand requirements in the long term.

Achieving good predictability of demand, both in terms of timing and volume, is critical to optimise the use of available supply in the short term and advise on longer-term supply needs. While it is unclear what demand volume will be associated with targeted vaccination activities to address immunity gaps, preliminary analysis suggests such targeted vaccination needs would represent less than 10% of the overall demand over 2025–2030. Updating policy recommendations to avoid backsliding on the achievements of the EYE Strategy will help strengthen the demand forecast and improve communication of supply needs to industry.

TARGET OUTCOMES

1. Improved demand predictability in the short and medium terms for outstanding routine introductions and ongoing/future PMVCs.
2. Clarified long-term demand requirements for targeted vaccination campaigns beyond routine immunisation and PMVC needs to inform UNICEF procurement strategy, with the generation of a granular forecast by end 2024.

INTERVENTIONS

- Prioritise country engagement on planning campaign phasing and outstanding routine immunisation introductions, for optimal planning of available supply.
- Advocate for and support the definition of clearer targeted vaccination campaign policy recommendations.
- In a scenario where targeted vaccination campaigns are recommended, identify funding sources for such activities, quantify scope/timing and engage with countries to reduce demand forecast volatility to help support manufacturers' production planning.
- Under ICG guidance, starting in 2025, undertake outbreak forecast modelling, considering short- and medium-term time horizons, and risks associated with urbanisation and climate change; and outline implications for stockpile sizing.

Objective 2 – Achieve a supplier base, which in the medium term minimises country plan disruptions due to any manufacturer supply adjustments, and over the long term is diverse and sustainable.

While Objective 1 of this roadmap aims to alleviate some of the uncertainties related to the demand forecast, it is equally important to provide a clearer picture of what a sustainable and diverse supplier base would look like in the future to guide manufacturers' decisions and avoid unintended consequences such as premature market exits or worsening of supply terms (e.g. spikes in pricing or slower/unreliable delivery schedules), in a context of waning PMVC activities.

It is worth noting here the opportunity the YFV market provides to contribute to the broader objectives of strengthening vaccine supply resilience at regional levels, specifically in Africa where the COVID-19 pandemic exposed the vulnerability and inequity of access to vaccine supply; and accelerating access to vaccines in future outbreaks or pandemics. Institut Pasteur de Dakar (IPD) is the only manufacturer on the continent producing drug substance of a WHO-prequalified vaccine, with investments in manufacturing capacity covering various antigens and vaccine platforms. On the basis that YF has high strategic importance for the African continent, YFV was designated as a Priority vaccine under the African Vaccine Manufacturing Accelerator (AVMA), making YFV manufacturers on the African continent eligible for AVMA subsidies. From a global market health perspective, the AVMA Priority vaccine designation did not imply that the YFV supplier base objectively required an additional or Africa-based supplier. Despite the exposure to geopolitical risk in the near term, the YFV supplier base happens to be the most geographically diversified of all Gavi-funded vaccine markets, in addition to being likely headed towards a large global overcapacity situation.

TARGET OUTCOMES

3. Diversified global supplier base of WHO-prequalified YFV to serve global and Gavi-eligible country demand with total capacity, including buffer capacity, that can sustainably meet long-term demand requirements (routine and outbreak response). To serve Gavi-eligible countries, this translates into the following targets:
    a. Minimum of two suppliers of WHO-prequalified YFV released by different National Regulatory Authorities (NRAs).
    b. Minimum 25% buffer capacity over the base case steady-state demand projection (which doesn't account for targeted vaccination campaign needs) – i.e. a minimum total supply capacity of 60 million doses available to Gavi-eligible countries.
4. No country plan disruptions in the medium term (due to any manufacturer supply adjustments) by implementing timely and relevant mitigants.

INTERVENTIONS

- Based on progress made under Target Outcome 2, refresh analysis informing Target Outcome 3 (i.e. redefine supply targets based on demand scenarios and country plans linked to targeted vaccination campaigns), thereby ensuring procurement and manufacturer engagement activities can effectively communicate demand forecast updates and supplier base needs over the longer term.
- From 2026 onwards, ensure no overreliance on a single supplier in the Gavi/UNICEF portfolio to mitigate against the aggregate of risks carried by individual suppliers, taking into account trade-offs related to, for example, cost-effectiveness or supply reliability.

- Continue close engagement with manufacturers to monitor supplier-specific risks (including geopolitical risk, supply capacity ramp-up, delivery performance, business sustainability thresholds, etc.) and their supply reliability, and undertake relevant interventions in response to identified risks.
- Through continuous supplier engagement, including the UNICEF tender process, provide support to relevant manufacturers to sustainably and timely transition or adjust manufacturing capacities to meet the long-term demand requirements.
- Monitor progress of pipeline supply to assess longer-term supplier base evolution.

Objective 3 – Preferred products remain available, in a context of longer-term demand variations, contributing to increasing coverage and minimised wastage.

The YFV characteristics of lifelong protection with a single-dose regimen are very supportive of market health; and the Alliance's focus should be to maintain this highly desirable product profile, even as the market evolves and demand declines in the longer term. Regarding specific presentations, further efforts to reduce cold chain requirements by switching all vaccines from ampoule to vial presentations may contribute to strengthening countries' implementation capacity. Finally, the role of vero cell candidate vaccines remains to be defined, and how they might further contribute to meeting countries' product preferences.

TARGET OUTCOMES

5. A balance of different YFV presentation uptake that maximises coverage and minimises wastage.
6. Established potential role of vero cell candidate vaccines for a healthier market.

INTERVENTIONS

- Work with countries on portfolio optimisation to support uptake of five-dose vials where relevant, and support rational switches.
- Ensure presentation-specific supply availability through regular supplier engagement and sharing of demand forecast.
- Monitor impact of portfolio optimisation on wastage/coverage to inform programmatic support/guidance.
- Understand and articulate value of vero cell candidate vaccines from the perspective of safety, efficacy, programmatic use, wastage, coverage, etc.
- Gauge country interest and preference for vero cell candidate vaccines. If programmatically preferable, consider impact on Gavi support and market dynamics; and revisit the market shaping strategy in the longer term.