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The Market Shaping Goal

Ensure healthy markets for vaccines and related products

Gavi Alliance Market Shaping Roadmap for *Typhoid Conjugate Vaccines (TCV)*

Public Summary
October 2022

Purpose and scope

The roadmap is a foundational tool of Gavi's market shaping strategy with the purpose of articulating a mid- and long-term 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 objectives, target outcomes and interventions articulated in this roadmap focus on:

- The Gavi74 [1] market while including global market considerations to highlight interdependencies and their impact on overall market health
- Maintaining a secure and sustainable market for Gavi countries as demand ramps up and pipeline vaccines come to market

Current epidemiological context of Typhoid and Gavi engagement

Typhoid fever is a systemic illness caused by Salmonella enterica serovar Typhi. An estimated 11 to 21 million cases of febrile illness and 117,000 to 161,000 deaths are attributed to the disease each year[2]. As typhoid affects populations without access to safe water, improved sanitation, and safe food, it is a public health concern for millions of people in Gavi supported countries, particularly those in the most marginalised populations. Data reviewed by the WHO Strategic Advisory Group of Experts on Immunization (SAGE) indicates that a major burden of severe disease occurs in younger age groups where 27% of all typhoid disease occurs in children under five years. There is an increasing number of cases that are antimicrobial resistant (AMR) as the disease readily becomes resistant to the common drugs used for treatment. Large scale vaccination strategies for typhoid are expected to reduce the burden of illness, especially the incidence of multi drug-resistant and extensively drug-resistant typhoid, by reducing the levels of circulating bacteria that are resistant to antibiotics and by reducing the number of patients being prescribed antibiotics.

In 2018 WHO released a position paper for the Typhoid Conjugate vaccine following the prequalification of the Vi Capsular Polysaccharide-Tetanus Toxoid Conjugate Vaccine. The Gavi Board[3][4] then approved support for the introduction of TCV as a routine programme, with a single dose at 9 or 15-18 months, and a catch-up campaign at the time of introduction with a target population of 9 months – 15 years old. Gavi also offers support to use TCV to respond to confirmed Typhoid outbreaks. As of May 2022, four countries[5] from the Gavi74 had introduced TCV and one more is approved for support and planned for early 2023. Between 2019 and 2021, over 57 million Gavi supported doses of TCV were shipped.

Market evolution over the next 10 years

The WHO Global Market study for TCV estimates mid-term demand for TCV globally to range from 43M to 163M doses per year (moderate estimate of 111M doses per year) and expects demand to decrease in the long-term to 22M–96M doses per year (moderate estimate of 71M doses per year) once the one-time campaigns have been conducted. According to the report, non-Gavi demand may be slow to materialize and modest in size, and this may depend on availability of typhoid burden and typhoid AMR resistance data.

For Gavi74, mid-term demand is currently estimated 50-60M doses in the medium demand scenario (blue line in figure 1), but low and high scenarios range from 20M doses to 150M doses. The current forecast trajectory follows the blue 'medium' scenario. India is assumed to expand its TCV programme nationally in the high scenario (approximately 20M doses per year) with a subnational catch-up campaign (targeting 25%

[1] 74 Gavi-supported countries including currently eligible, transitioning, and transitioned countries
[2] Antillon et al (017), Stanaway et al (2017), Buckle et al (2012), Mogasale et al. (2014) and WHO (2019)
[3] Gavi Board meeting November 2017. Support for TCV
[4] In December 2021, Gavi Board approved a second investment in Typhoid of $13m for diagnostic tools to better match TCV use to areas with Typhoid burden
[5] The four countries that have introduced TCV are: Pakistan, Liberia, Zimbabwe, Nepal; and Malawi is approved for introduction

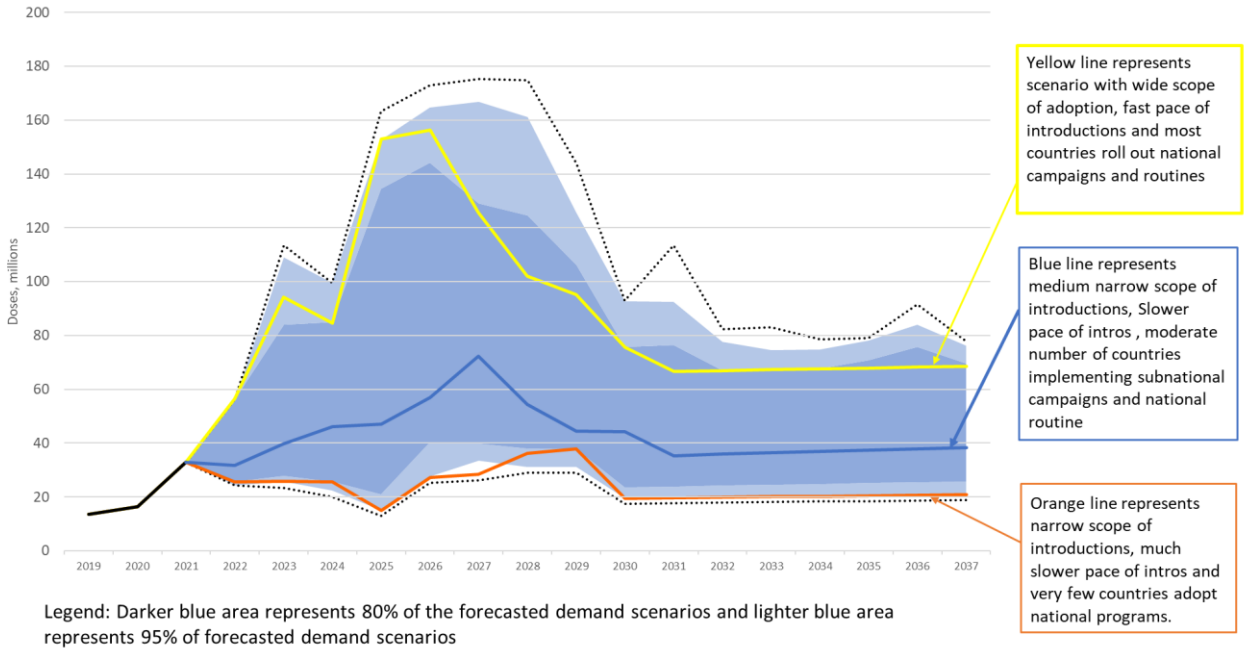
of the campaign cohort approximating to 80M doses administered over four years)[6]. Long term annual demand is estimated to settle between 20M doses and 70M doses once one-time campaigns are completed, with a base case of approximately 40M doses.

The TCV market is still relatively immature, and uncertainty is therefore high regarding uptake and introduction of TCV. Early introducing countries have typically been those in which substantial burden of disease and where data have been available to support the rationale for TCV introduction. Factors driving variability of demand forecasts include assumptions on national vs. targeted immunisation strategies, lack of reliable burden data to support country decision-making, potential future improvements in water and sanitation, competing priorities for countries, probability of outbreaks, as well as less Gavi support and fiscal space due to impending transition for some countries.

All early introducing countries have elected for a national TCV introduction strategy (routine and catch-up campaign), though very large countries which influence future demand more significantly may opt for risk based TCV strategies, particularly for the catch-up campaign component of TCV introductions. India, for example, accounts for almost half of the global death burden due to Typhoid fever and is expected to introduce in the short to mid-term given a 2022 recommendation by India's National Technical Advisory Group for Immunisation. In 2019, approximately 340,000 doses were used for outbreak response in Zimbabwe, with further outbreaks possible.

The magnitude and the duration of the Covid-19 pandemic impact on immunization programmes and TCV demand is still uncertain. Impact on immunisation has varied across Gavi countries, but disruptions were less severe in 2021 compared to 2020. From 2023 onwards the forecast assumption is for a return to 'normal' activity levels for routine immunisation. However, the emergence of new Covid strains, national lockdown measures, export restrictions, and cold chain capacity constraints have potential to disrupt demand and supply further.

Figure 1: Gavi74 TCV base demand forecast 2022



Legend: Darker blue area represents 80% of the forecasted demand scenarios and lighter blue area represents 95% of forecasted demand scenarios

The global supply base for TCV from two incumbent suppliers is sufficient to meet current and future demand in the **medium demand** scenario (blue line in figure 1). In a high demand scenario (yellow line in figure 1), where there are demand peaks due to one-time campaigns, forecasted supply capacity from incumbent

[6] Forecast and relevant assumptions finalized in December 2021 and the June 2022 recommendation for TCV introduction in India by the National Technical Advisory Group for Immunization may impact this forecast.

suppliers will likely be able to meet demand levels for several years, provided early demand signals are communicated to manufacturers to scale up production. However, in both the base and high scenarios the market would benefit from new entrants providing additional supply security and diversifying the supplier base. Catch-up campaigns will need to be planned carefully over the next several years to ensure that their timing, size and pace are manageable in the context of absolute capacities and planning lead-times faced by incumbent suppliers before additional manufacturers enter the market or incumbents scale up.

Bharat Biotech International (BBIL)'s Typhoid conjugate vaccine was prequalified in 2017 and was the first TCV on the Gavi menu. At the end of 2020, Biological E Limited (BioE) gained WHO PQ and was added to the menu. Both vaccines are conjugate vaccines in a 5-dose vial, containing Vi polysaccharide of Salmonella typhi Ty2 conjugated to either tetanus toxoid for BBIL's product, and a carrier protein (CRM197) for BioE's product. Despite the two products not being identical (for example differences exist in thermostability labelling, carrier proteins and overall data sets) the two products are designated by WHO to be broadly interchangeable and therefore UNICEF allocates products based on market dynamics when countries apply to introduce TCV. The appropriateness of the interchangeability characterizations in markets requires regular monitoring. From 2024 to 2029 the supplier base is expected to expand with arrival of one or two additional manufacturers of prequalified vaccines with similar profiles to the current vaccines.

Gavi73 healthy market dynamics and challenges over the next 10-years

TCV Market health assessment 2022

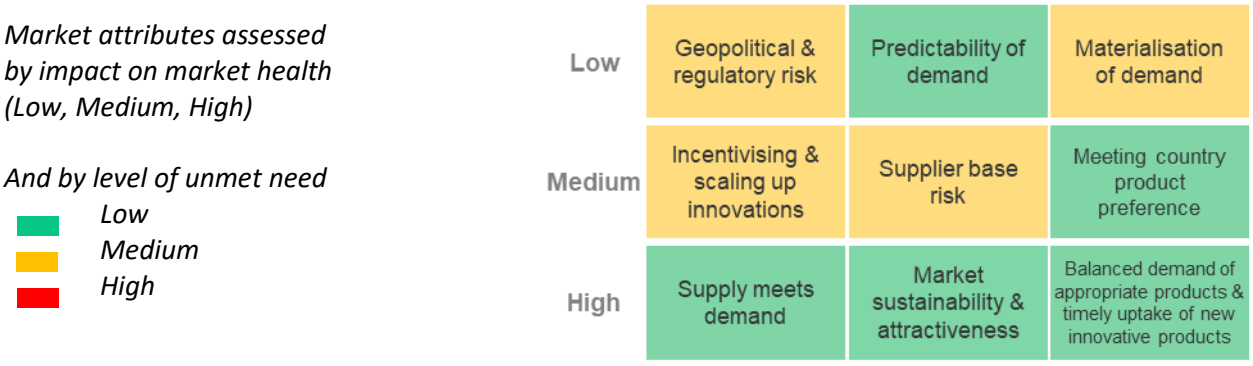


Figure 2: Assessment of healthy market attributes for TCV (2022), based on the Gavi Alliance Healthy Market Framework

The TCV roadmap covers a period of 9 years (2022 – 2030) which can be divided into three phases based on supply and demand dynamics (or market lifecycle stages):

- Short-term (2022 – 2023): Market health in Gavi 73 is expected to be moderate in 2022 **with four healthy market attributes met and five attributes partially met.** The TCV market is still immature (with four country introductions to date) and therefore future introduction **and uptake of TCV is relatively uncertain** and must remain a key focus for the Alliance.

  Supply currently meets demand, and the market is expected to be served predominantly by the two incumbent suppliers, BBIL and BioE, with **surplus supply capacity of prequalified vaccines**. There are multiple pipeline candidates, which have likely been incentivised to market by the widespread disease burden, the large target cohorts for introduction and catch-up campaigns, and expectations regarding long-term steady-state routine demand and increasing antimicrobial resistance.

- Mid-term (2024 – 2029): During the next phase in 2024-2029, market health is expected to improve, characterized by **an enlarged supplier base** with at least one additional prequalified

vaccine becoming available for supply from a **country of production outside of India,** and better visibility on future introductions including from former and never Gavi eligible MICs. However, demand materialization and predictability may remain a challenge as well as supplier sustainability.

- Longer term (from 2030 onwards): TCV market **demand is likely to start decreasing to a steady state of routine programme demand only**, due to the expected end of campaign volumes once the majority of countries have introduced. There will be a need to manage **the possibility of market exits** of suppliers and ensure sustainability of the supplier base.

Strategy to sustainably improve market health

Gavi Partners defined a long-term strategy for the typhoid conjugate vaccine market to address these challenges, which translates into the following strategic market objectives and target outcomes:

Objective 1: Timely demand materialization in the short to medium term (0-8 years) and optimised long-term demand predictability
Demand materialization and predictability will be important to both sustain and attract new suppliers.

➢ Target Outcome 1: Predictability and materialization of demand is enhanced by leveraging up to date assumptions, programmatic guidance and ensuring greater visibility of forecasts

Objective 2: Supply meets demand in the short to medium term (0-8 years), supplier base diversifies during the mid-term (2024-2029) and remains sustainable over the long-term
2022 volumes will be supplied by two Indian manufacturers, BBIL and BioE. To balance future supply security as demand increases, a diversified supplier base will be desirable.

➢ Target Outcome 2: Sufficient supply availability from PQ manufacturers allows timely introductions

➢ Target Outcome 3: Supplier duopoly dependency comes to an end by ensuring at least 1 new supplier enters the market and maintenance of diversified supplier base with at least 3 manufacturers supplying to UNICEF in the mid term

➢ Target Outcome 4: Supply security is ensured while managing expected overcapacity in terms of manufacturer expectations once market volumes reduce to routine demand in the long term from 2030 onwards

A concerted action plan ensures the coordination between Gavi market shaping partners and facilitates the achievement of the above strategic market outcomes. Actions include the following:

- Leverage core and extended Alliance partners to support countries to assess data requirements for decision making, selection of vaccination strategy, applications, introduction planning, and sustainability to support demand materialization
- Incorporate evidence as it becomes available on impact of TCVs, impact and feasibility of subnational campaigns, co-administration, timing of vaccination, country interest, etc. into forecasts to narrow the range of the demand forecast and ensure timely communication with manufacturers, engaging with partners and countries on long-term planning.
- Develop WHO guidance to inform countries on available prequalified TCV product information and product equivalence addressing questions related to differences in biological features of vaccines
- Manage demand and country expectations by scheduling and pacing catch-up campaigns in a manner that allows scale-up in line with supply availability

- Engage closely with suppliers to manage expectations around supply capacity in case of high demand scenarios, understand potential risks of low demand in the short term, and overcapacity in the long term. Identifying mitigation strategies to maintain both current suppliers' and pipeline manufacturers' interest in the market. Support one or more new TCV manufacturers to obtain WHO prequalification depending on the shape of demand (e.g., through additional investment, improving visibility into demand, etc.)

Objective 3: Achieve sustainable TCV price levels for the future supplier base and Gavi countries.

While the incumbent suppliers have created a competitive landscape, relieving both Gavi's and beneficiary countries' vaccine budgets, the TCV market attractiveness needs to be retained for pipeline manufacturers. Therefore, while affordability is critical, future trade-offs need to be aligned to price levels that would be sustainable for a more diversified supplier base.

➢ Target outcome 5: Maintain affordable and sustainable weighted average price in the short to mid-term

A concerted action plan ensures the coordination between Gavi market shaping partners and facilitates the achievement of the above strategic market objectives. Actions include the following:

- Engage existing and pipeline manufacturers to identify appropriate activities that support product affordability and further explore the value of procurement tactics to harness emerging competition

Objective 4: Appropriate and innovative vaccines features are identified

➢ Target Outcome 6: Establish new target features of an improved TCV based on programmatic evidence currently being generated leading to potential R&D investments by manufacturers

A concerted action plan ensures the coordination between Gavi market shaping partners and facilitates the achievement of the above strategic market outcomes. Actions include the following:

- Review evidence-based studies to understand the value of various product innovations and relay back to manufacturers to guide improvement in product characteristics including but not limited to lower control chain requirements, multivalent and combination vaccines and novel antigen delivery methods (e.g. microarray patches).