

GLOBAL MARKET STUDY MALARIA VACCINE

Key Takeaways

- A first malaria vaccine is currently implemented in a pilot programme in selected areas of Ghana, Kenya and Malawi. Data from the programme will be reviewed by WHO in the last quarter of 2021 to inform a potential recommendation for broader use of the vaccine in children in sub-Saharan Africa.
- The first vaccine could be WHO pre-qualified in the first half of 2022. A second vaccine started Phase 3 trials in mid-2021.
- It is expected there will be high demand for a malaria vaccine. However, supply will be the constraining factor through the medium term (4-6 years from the expected first introductions in 2023). Moreover, there is risk of supply concentration with one main supplier in the long term. Finally, as these malaria vaccines are being developed specifically for use in children in sub-Saharan Africa, they do not have a market in high income countries. This is a challenge for recovering past and ongoing investment costs.
- Action is required by WHO and other global and regional partners, manufacturers and countries in order to address market imbalances, support development of a healthy malaria vaccine market and ensure timely access. Actions include supporting countries' decision making, planning and preparations; and working with manufacturers, procurement and financial schemes to increase supply capacity.

QUICK STATS

NUMBER OF VACCINE PRODUCTS¹

2

NUMBER OF VACCINE PRODUCTS WHO PRE-QUALIFIED

0

TOTAL NUMBER OF MANUFACTURERS

2

2021 ESTIMATED GLOBAL SUPPLY

1.4M doses

2021 ESTIMATED GLOBAL DEMAND

1.3M doses

ESTIMATED STEADY STATE DEMAND

~110M doses per year

EXPECTED PRICE PER DOSE

US\$ 2.00-10.00

Purpose & Background

Much progress has been achieved in terms of malaria disease reduction in the last 20 years, by layering different malaria control interventions. However, progress has plateaued since 2015². WHO estimates that there were 215 million malaria cases and 386,000 deaths in sub-Saharan Africa in 2019. 70% of deaths were in children under the age of five.

A malaria vaccine added to existing malaria prevention and treatment tools is expected to considerably reduce morbidity and mortality. The first malaria vaccine (RTS,S/AS01E) is currently implemented in routine immunization programmes in selected areas of Ghana, Kenya and Malawi as part of the Malaria Vaccine Implementation Programme (MVIP). Data from the MVIP will be reviewed by the Strategic Advisory Group of Experts on Immunization (SAGE) and the Malaria Policy Advisory Group (MPAG) in Q4 2021 to inform a potential WHO recommendation for broader use of the vaccine in children in sub-Saharan Africa.

Meanwhile, there are another 102 studies underway for malaria vaccine development, although most (91%) are in the discovery, pre-clinical or Phase 1 stage.

This market study was initiated in order to help establish a common understanding of the malaria vaccine market in the near and long term (2022-2036) and to support timely access to the vaccine should there be a WHO recommendation for broader use of RTS,S/AS01E. The study focuses on vaccines targeting *Plasmodium falciparum* (the deadliest species for humans),

¹ Based on the criteria in the market study.

² WHO, World malaria report 2020.

provides an overview of projections of potential programmatic dose requirements (demand), product landscape and projected supply, and suggests actions WHO and partners should take to enhance market conditions and expand vaccine access.

Demand

Malaria vaccine demand is concentrated in sub-Saharan Africa; this is where the highest burden of *Plasmodium falciparum* malaria disease lies.

The estimates of programmatic dose requirements are based on the Gavi Strategic Demand Scenarios (SDS)³ using the following assumptions:

- Vaccination in administrative areas in which *Plasmodium falciparum* parasite prevalence (in 2–10 years old) is >10%
- Coverage estimates anchored on the first dose of measles-containing vaccine (MCV1)
- 4 doses administered through the routine immunization programme (first 3 doses from 5 months of age, one month interval between doses; 4th dose 15-18 months after administration of 3rd dose)
- Potential additional annual doses until 5 years of age, in settings where the transmission of malaria is highly seasonal
- Absence of defined Gavi programme design

Three demand scenarios (all supply and financially unconstrained) were modelled in the Gavi SDS:

- Higher scenario assumes higher pace of adoption (30 countries), higher number of surviving infants, higher coverage, 15% drop-

out between dose 3 and dose 4 and 15% wastage;

- Medium scenario assumes medium pace of adoption (25 countries), medium estimate of surviving infants, lower coverage compared to the higher scenario, 20% 4th dose dropout, and 10% wastage;
- Lower scenario assumes lower pace of adoption (20 countries), lower number of surviving infants, lower coverage compared to the medium scenario, 25% 4th dose dropout, and 5% wastage.

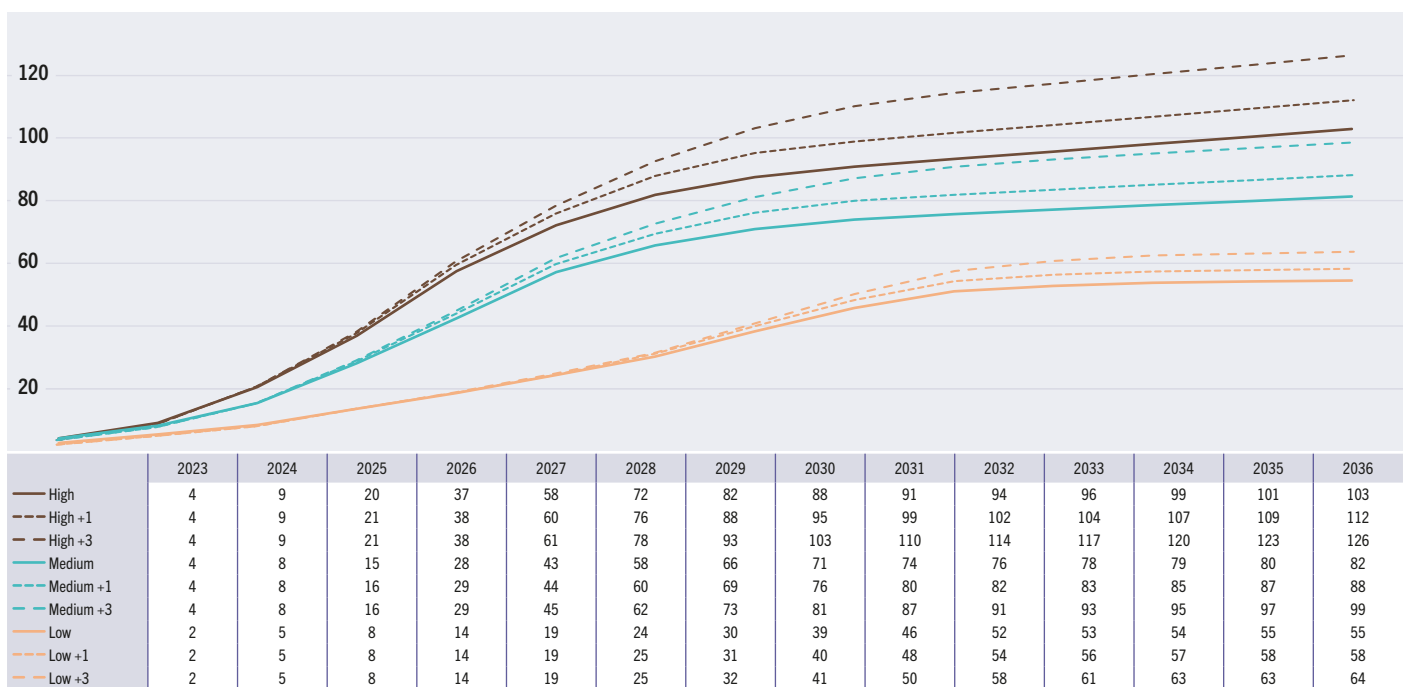
Potential demand for seasonal doses (one and three) were added to each scenario. All scenarios were used to estimate the Supply / Demand balance.

In all scenarios, demand beyond the MVIP is expected to materialize from 2023.

Although there is demand uncertainty due to the unique vaccination schedule, potential subnational strategies and potential seasonal use; and noting that the optimal mix of malaria interventions and programme design are still to be defined, the estimated steady state demand by 2036 is approximately 110 million doses per year (based on the high scenario with 1 additional seasonal dose).

Various consultations and analysis of fiscal space and past introduction history were conducted. The work showed that there is likely to be high demand. The main drivers of demand evolution are the number of countries introducing each year, especially large countries. The analyses also highlighted that some countries, while affected by high malaria disease burden, may need support related to decision making and planning (especially around fiscal space planning and sequencing of new vaccines). The malaria vaccine will be an additional intervention for which countries will need to plan.

FIGURE 1: COMPARISON OF DEMAND SCENARIOS, INCLUDING ADDITIONAL SEASONAL DOSES (IN MILLIONS OF DOSES)



3 Draft Gavi Strategic Demand Scenarios (SDS), as of June 2021, including additional seasonal doses.

Supply

Consultations with manufacturers and experts, as well as a review of publicly available information on malaria vaccines, provided the basis for an assessment of the future supply of malaria vaccine. The study focuses on vaccines targeting mortality or morbidity reduction in children under the age of 5 and vaccines licensed or at least approved for Phase 3.

As a result, two products were identified for inclusion in the full analysis of the market study ⁴, RTS,S/AS01E and R21/Matrix-M, as summarized in Figure 2 below.

As neither of the products included in the market study have full marketing authorisation nor WHO pre-qualification, the estimated timing of such is a key factor in assessing supply.

Supply capacity is based on both antigen and adjuvant availability, which means that while there are expected to be two manufacturers with marketing authorization for these products, two additional manufacturers will be involved in the production and therefore will impact the supply availability.

It is expected that supply availability will not ramp up significantly until the medium and long term. Factors such as demand certainty, financing and a sustainable business model, as well as timing of licensure and availability of the second vaccine, are important for realizing this supply. Moreover, special interventions would likely be needed to further improve availability and the future health of the malaria vaccine market, including a balanced split between the two products in the longer term.

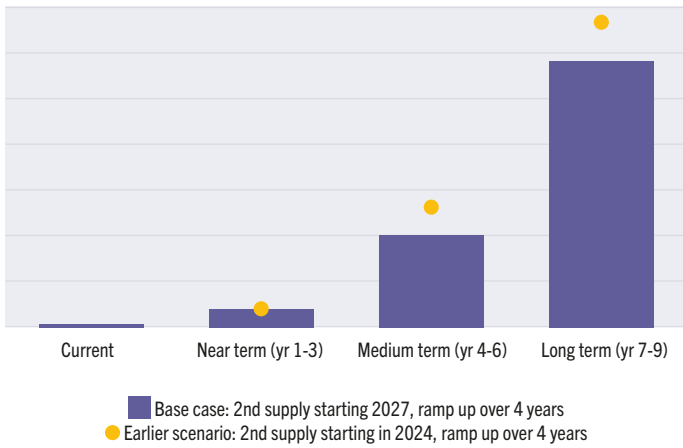
FIGURE 2: SUMMARY OF MALARIA VACCINE PRODUCTS INCLUDED IN THE FULL MARKET STUDY

| Vaccine product | RTS,S/AS01E (GSK & BBIL from 2029) | R21/Matrix-M (SII) |
|---------------------------------|--|--|
| Status | Positive Scientific Opinion (Article 58) from the European Medicines Agency (EMA) in July 2015. Pilot implementation in Ghana, Kenya and Malawi as part of the MVIP on-going. Phase 4 studies as agreed with EMA on-going. | Phase 3 trial across 5 sites, 4,800 children, aged 5-36 months, initiated in Q2 2021, on-going. |
| Estimated WHO pre-qualification | Possible in mid-2022, assuming a WHO recommendation for broader use is provided in Q4 2021. | 2026/2027 (5-6,5 years from start of Phase 3 trials, based on the expected timelines for administration and follow-up of the proposed 4-dose schedule, a standard but streamlined WHO pre-qualification (not including any additional programmatic or technical reviews). However, University of Oxford (UofO) and Serum Institute of India (SII) have publicly indicated their intention to pursue a fast-track timeline, with the ambition of product licensure and availability for use by end 2023 / 2024. Both scenarios are included in the below supply scenarios ("Base"- the streamlined timeline, and "Earlier"- the companies' stated fast track timeline). |
| Schedule | Perennial settings (as per WHO recommendation for use in pilot implementation): Vaccination in children from 5 months up to 17 months of age (at first dose): » 3 doses with 1-month intervals, 4th dose recommended 15-18 months after 3rd dose. Phase 3 trial in seasonal settings on-going to assess impact of annual doses in children up to 5 years of age before the rainy season ⁵ . Soon to start case control study to evaluate incremental value of the 4th dose compared to a 3-dose course. | Perennial and seasonal settings (in Phase 3 trials): » 3 doses with 1 month interval at 5, 6 and 7 months of age, 4th dose given 12 months after 3rd dose. » The relevance of a 5th dose is being studied as a part of the Phase 2 and 3 trials. |
| Presentation | 2-dose vials (2 clipped vials - 1 vial for antigen (lyophilized), 1 vial for adjuvant). 0.5ml/dose once reconstituted | 1-dose vials (2 vials - 1 vial for antigen, 1 vial for adjuvant). 0.5ml/dose once reconstituted Other options under consideration (e.g., multi-dose vial, 2 vials; single dose vial that combines adjuvant & antigen) |
| Main production responsible(s) | RTS,S antigen: GSK (through 2028) RTS,S antigen: Bharat Biotech International Ltd (BBIL) (from 2029) AS01E adjuvant: GSK | R21 antigen: SII Matrix-M adjuvant: Novavax |

⁴ At the time this study was being finalized in late July 2021, BioNTech announced their intention to start clinical trials in 2022 of a vaccine to prevent malaria, using similar technology to their Covid-19. Analysis of this potential candidate vaccine is not included in this report.

⁵ Daniel Chandramohan et al. Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention. N Engl J Med 2021; 385:1005-1017

FIGURE 3: EXPECTED RAMP UP OF SUPPLY AVAILABILITY BASED ON CURRENT INFORMATION (“2ND SUPPLY” INDICATES SECOND SUPPLIER)



A third product, the PfSPZ vaccine from Sanaria, is also in development targeting the *Plasmodium falciparum* parasite species.

This vaccine has a different profile targeting disease elimination with an initial use case targeting travelers to sub-Saharan African and subsequently children and adults (2-50 years of age) in Africa. Next generations of this vaccine are also under development, in order to allow for larger volumes in order to support an elimination goal.

While there are plans for the PfSPZ vaccine to target children under the age of 2 in the future, this age group is not included in the current planned Phase 3 trial due to lack of efficacy (e.g., no T-cell response) in children under 2 years of age in Phase 2 trials⁶. In order to align with the demand assumptions based on children under 2 years of age and due to the uncertain timeline for the vaccine to be assessed for this age group, the PfSPZ vaccine was not included in the subsequent analysis on supply and supply-demand balance.

Supply / Demand Balance

A number of factors have contributed to assessing a future supply / demand balance for malaria vaccine. Although not yet fully introduced in any country, demand for a malaria vaccine is expected to be high and, materialization of this potential demand is expected to be limited by supply availability through the medium term (4-6 years from the expected first introductions in 2023).

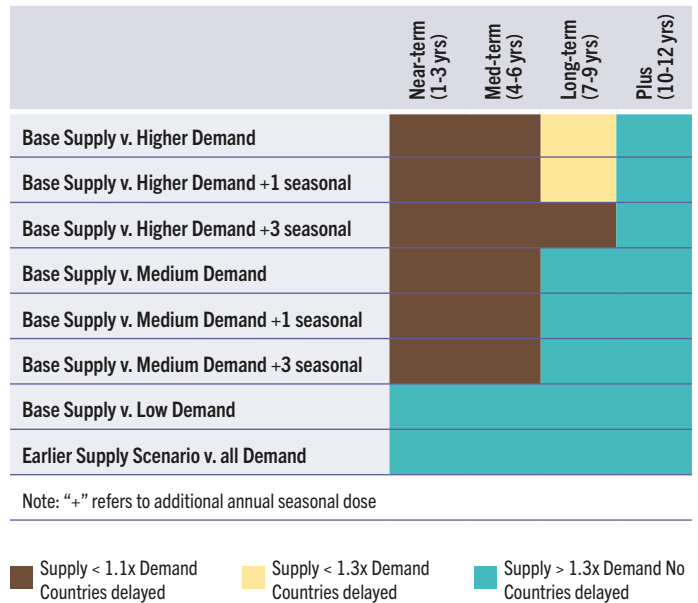
It is expected that the supply will be insufficient through the medium term for the medium and high demand scenarios, with a constrained supply potentially during the first 6 years following expected first introductions in 2023. This could potentially extend to 9 years should there be demand for up to 3 additional seasonal doses or if no action is taken to further improve supply availability.

Furthermore, if the assumptions for timing of the introduction of both vaccines are confirmed, and there are no interventions and no

additional market entries, the market will be concentrated through the next 15 years (through 2036), with one supplier representing more than 70% of the projected supply.

In addition to the supply / demand imbalance and supply concentration, other factors should be taken into account for long-term supply sustainability and market health. For example, contracting volumes across suppliers that are balanced and sustainable, encouraging price competition and product innovation, and regional diversification of the supplier base with a potential focus on manufacturing in Africa.

FIGURE 4: SUPPLY / DEMAND BALANCE (FROM 2023)



Price

As there is no commercial market yet for a malaria vaccine, it is difficult to provide firm estimates on price. Statements on pricing have indicated a commitment to price the vaccine at manufacturing cost plus a margin generating a return of no more than 5% (GSK) and a very cost-effective price (SII).

- Price range used in cost effectiveness studies of \$2.00 - \$10.00 per dose.
- Achieving price in the lower part of the range may require external intervention, including to cover the cost of investment in increased capacity, guarantee demand volumes, and encourage competition between manufacturers.

As these malaria vaccines are being developed specifically for use in children in sub-Saharan Africa, they do not have a market in high income countries which can be a challenge in terms of recovering past and ongoing investment costs.

⁶ Martina Oneko, et. al. Safety, immunogenicity and efficacy of PfSPZ Vaccine against malaria in infants in western Kenya: a double-blind, randomized, placebo-controlled phase 2 trial. Nature Medicine 2021; Vol 27: 1636-1645.

Areas for Action

In order to support the development of a healthy malaria vaccine market, WHO will collaborate with its partners to:

- Support countries on decision-making, planning and introduction preparations, with special consideration for large countries and countries transitioning from Gavi support.
- Provide visibility into supply outlook and develop an approach to prioritizing distribution of limited supply in initial years.
- Continue to provide visibility into regulatory and policy and programmatic requirements for WHO pre-qualification.
- Work with manufacturers, governments, procurement and financing schemes to incentivize an increase in supply capacity, and regional diversification of the supplier base, with a potential focus on manufacturing in Africa.
- Use a coordinated project approach to monitor and communicate key milestones to maximize vaccine access by countries.

Methodology & Resources

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, European Commission, China CDC, Thailand National Vaccine Institute, UNICEF SD, PAHO RF, WHO EURO, Gavi, and the Bill & Melinda Gates Foundation, along with manufacturers associations (DCVMN and IFPMA) and independent experts. Additionally, a malaria expert joined this MI4A Advisory Group. Industry representatives and other stakeholders were invited as observers.

Supply resources:

MI4A annual data collection from manufacturers, bilateral discussions with manufacturers and partners review of clinical trials information, review of regulatory pathway assumptions.

Demand resources:

Gavi SDS supplemented with other analysis, MVIP coverage data, discussion with WHO Global Malaria Programme, WHO Malaria Vaccine Implementation Programme and PATH

Other Useful Public Resources

[WHO position paper: Malaria vaccine, January 2016](#)

WHO Preferred Product Characteristics (PPC) for Malaria Vaccines. WHO/IVB/14.09, November 2014 (<https://apps.who.int/iris/handle/10665/149822>) (update under development)

Gavi statements on malaria vaccines:

- [New financing agreement boost for malaria vaccine](#)
- [Partnership welcomes launch of first malaria vaccine pilot](#)

Disclaimer: This market study was completed before the longer-term impact of the SARS-CoV-2 pandemic was fully ascertained, e.g., overall impact on demand. However, as broader roll-out of the malaria vaccine is not expected to occur until 2023, it is assumed that the acute phase of the SARS-CoV-2 pandemic will not impact demand. An update to elements of the market study will likely be needed if key assumptions change.

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