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New malaria vaccines: what they can and what they cannot change for the global malaria pandemic

SYNTHESIS

Funding and progress against malaria began plateauing in 2015. More recently, the trajectory even reversed under the combined effects of several crises—the Covid-19 pandemic, biological threats such as antimicrobial resistance, the acceleration of climate change, and inflation. There were an estimated 249 million malaria cases in 2022 – 5 million more cases than in 2021, 9 million more than in 2020, and 20 million more than in 2019.

A new impulse in the global fight against malaria was given in October 2023, when an update of WHO recommendations opened the way for the large-scale roll out of two malaria vaccines: RTS,S and R21. WHO recommended that malaria vaccines are introduced as additions to, not substitutes for, other existing and innovative malaria tools – such as new generation dual-ingredient nets, seasonal chemoprevention, indoor residual spreading, or prompt diagnosis and treatment. The vaccine was recommended for children from 5 months of age in settings of moderate to high transmission of *Plasmodium falciparum*, the specific parasite species targeted by the vaccine.

As demand for malaria vaccines by countries with endemic malaria has already reached very high levels[1], it is essential for policymakers and communities to develop a detailed, evidence-based understanding of what malaria vaccines can and cannot do. Such perspective is necessary to support the greatest impact from the use of the limited supply of malaria vaccines. It is also important to avoid counterproductive effects on the coverage of other malaria tools and other vaccines, through the repurposing of funding and capacities, or through the lower uptake of other anti-malaria tools. In the longer run, it is important to recognize that if community expectations about the impact of the malaria vaccine are set too high and unmet, it may fuel broader vaccine hesitancy.

The development of anti-parasitic vaccines is a major scientific breakthrough. Vaccines can boost the impact of existing malaria programs and save many more lives among children under five in settings of moderate to high transmission of *P. falciparum*, where nearly 25 million children are born annually. However, vaccines alone cannot put the international community back on track to reach the target of reducing the global malaria burden by 90% by 2030.

Existing scientific evidence shows that vaccines alone are not more efficient than other existing malaria tool. They do not fully protect eligible children from malaria infection, symptoms, and death; they are

[1] https://www.gavi.org/vaccineswork/malaria-two-groundbreaking-vaccines-have-been-developed-access-and-rollout-are

not recommended by WHO for pregnant women and fetus; and their price largely exceeds that of commodities for other malaria interventions. With the RTS,S vaccine, the protective effect appears to lead to a 20-30% reduction in clinical and severe cases over a multi-year period following the administration of the vaccine in young children between the ages of 5-17 months. The limited data on the R21 vaccine indicates a roughly 70% reduction in the number of cases in the 12-18 months after the vaccine was administered, and there is not yet sufficient data to evaluate its impact on cases over a longer period.

However, if rolled out alongside other malaria tools in an integrated manner, malaria vaccines have the potential to save many more lives among children under five in moderate to high transmission settings – mainly in subsaharan Africa – where 25 million children are born annually. A study evaluating the combination of RTS,S vaccination and administration of seasonal chemotherapy indicates that, when compared to the effect of each intervention on its own, the two interventions together can yield the massive boost of a 60-70% additional reduction in clinical cases, severe cases, and deaths.

Important knowledge gaps about the efficacy of each malaria vaccine exist and further research is needed . The most important knowledge gap is their impact on mortality. The RTS,S effectiveness study showed a 13% decline in mortality; however, the data released to date does not establish whether this decline was directly attributable to malaria vaccines or to other factors. As for R21, there is not yet sufficient data to evaluate its impact on severe cases and deaths. Other knowledge gaps that further research could address include the vaccines' impact on transmission, the efficacy of fewer than three doses in the primary series, and the impact of vaccine scale up on the uptake of other malaria tools in real-world implementation conditions.

From an implementation perspective, the roll out of malaria vaccines through existing child immunization platforms is expected to encounter general obstacles – such as global funding and supply constraints, insufficient human resources and other health system weaknesses – as well as vaccine-specific challenges - such as loss to follow up, vaccine hesitancy, cold chain weaknesses and the overall high vulnerability of immunization programs in crisis settings. Given the major difference between the efficacy of malaria vaccines and the more complete protection provided by several vaccines for other childhood illnesses, public health communication on the partial efficacy of malaria vaccines will be particularly important in order to ensure that communities continue to use other malaria prevention tools and seek timely care.

Initial guidance on prioritization of malaria vaccines vs other tools against malaria in real-world resource-constrained contexts is limited. Further evidence will need to be collected to support optimized public health impact of the available funding and capacities for malaria interventions as well as for other immunization programs, such as best strategies to reach children with insufficient access to malaria prevention tools, as well as more robust RTS,S and R21 cost-effectiveness evaluations.

At a macro-level, global funding constraints are the most important barrier to the deployment of malaria interventions and an urgent obstacle to be lifted. Despite tremendous efforts, the total funding gap for malaria control and elimination was estimated by WHO to reach 3.5 billion USD in 2020. . Over the past decade, domestic funding represented 31% of total malaria funding, and international funding represented 69%. Among the 11 countries that account for 70% of the global malaria burden, six are low-income countries whose restricted fiscal space and multiple human development challenges make it impossible for them to plug national malaria funding gaps with domestic resources: international funding is vital and yet insufficient to accelerate progress against the disease. While all are eligible for Global Fund grants, one is not eligible for Gavi financial support and two are due to transition away from Gavi support by 2032.

Gavi, Global Fund, and Unitaid are the three main multilateral global health institutions investing financial resources in the global fight against malaria. Their mandates are complementary. Malaria is one of the three diseases that Global Fund seeks to end by attracting, leveraging, and investing additional resources, as part of its effort to reduce health inequities and support attainment of the Sustainable Development Goals. The WHO recommendation on malaria vaccines has triggered the integration of malaria vaccines into the portfolio of Gavi, the Vaccine Alliance, an organization that focuses on supporting child immunization in low-income countries. Unitaid contributes to the global fight against malaria by making new health products available and affordable for people in low- and middle-income countries. All three organisations partnered to fund the large-scale RTS,S pilot evaluation on the vaccine's real-world effectiveness, an initiative coordinated by WHO.

The Global Fund accounts for 65% of all international financing for programs against malaria. Since 2002, it has invested more than 17.9 USD billion in malaria control programs and contributed to a 28% drop in malaria deaths in countries where it invests – where malaria deaths would have otherwise increased by 90% over the same period. In 2022, in countries where the Global Fund invests, 220 million nets were distributed, 37.1 million children accessed seasonal chemoprevention treatment, 14.6 million pregnant women received preventive therapy, 321 million suspected cases were tested, and 165 million cases were treated. For the 2023-2025 period, the Global Fund has mobilized a 4.2 billion USD envelope to invest in malaria programs, with unfunded country quality demand for malaria interventions still reaching 1.2 billion USD.

Gavi, the Vaccine Alliance, has started supporting 12 African countries to roll out of all 18 million existing doses of RTS,S vaccine. Access to malaria vaccines may accelerate when the large-scale production of R21 vaccine doses starts.[2] The cost of purchasing 4 doses of R21 vaccine for all eligible children would amount to approximately 280 million USD per year (840 million USD over 3 years).

Five years away from the 2030 target of a 90% reduction of the global malaria burden, the success of the Global Fund and Gavi replenishments in 2024 and 2025 will largely determine the level of international funding available for malaria interventions in low- and middle-income endemic countries between now and the Sustainable Development Goals deadline. Looking toward 2030 and beyond, in countries with the most constrained fiscal spaces, it will not be possible to accelerate and sustain progress against malaria with national financial resources alone–in these settings, there can be no transition away from external financial support mechanisms without elimination.

[2] Chad, CAR, DR Congo, Mozambique & South Sudan will be first to receive the R21 malaria vaccine with UNICEF deliveries starting in May, and with Uganda & Nigeria to follow. Information on the volumes of R21 to be distributed in 2024 have not yet been shared.

INTRODUCTION

Malaria is a blood-borne preventable and curable disease caused by a parasite (*P. falciparum* or *P. vivax*) that is transmitted by a mosquito vector. The millenary disease existed in Africa, Asia, Europe, and the Americas until the second half of the century, by which point most European countries and the United States were able to eliminate malaria with the massive use of DDT insecticide, causing damage to the environment and biodiversity.

Several countries, mainly in Asia and Latin America, have eliminated malaria in the recent decades[3]. Among the 80 countries in which malaria is endemic, approximately half are on a good track to achieve malaria elimination. Tremendous progress was also achieved between 2000 and 2015 in Africa, as the rate of malaria infections in Africa fell by 35% – with long-lasting insecticide treated nets estimated to have accounted for 68% of that reduction in cases[4] – and the rate of malaria deaths declined by 55% in the region.

These advances illustrate the impact of expanded vector control (i.e. insecticide-treated nets and indoor residual spraying) and improvements in parasite-targeting interventions (i.e. preventive chemotherapy and prompt diagnosis/treatment), largely funded by the Global Fund, who accounts for 65% of all international financing for programs against malaria. In 2022, in countries where the Global Fund invests, 220 million nets were distributed, 37.1 children accessed seasonal chemoprevention treatment, 14.6 pregnant women received preventive therapy, 321 million suspected cases were tested, and 165 million cases were treated.

Yet, progress against the malaria pandemic has stalled since 2015, for a variety of reasons including a major funding gap (the WHO estimates that an additional 3.5 billion USD was needed for malaria control and elimination in 2020) and biological threats (parasite resistance to drugs and diagnostics, vector resistance to insecticides, behavioural changes in the vector, and geographic expansion of certain vector species into new areas). Today, the malaria pandemic stands among the main killers of children under five and pregnant women where malaria is endemic with moderate to high levels of transmission.[5] In 2022, there were 269 million malaria cases and 608.000 deaths worldwide, with 94% of global cases and 95% of global deaths occurring in sub-Saharan Africa. Two countries, Nigeria and the Democratic Republic of Congo, account for over one-third of all global cases and deaths.[6]

The challenge of elimination and the burden of malaria remains greatest in Africa, where the epidemic faces the twin biological challenges of highly effective vectors (mainly *Anopheles gambiae s.l.*, *Anopheles funestus,* and *Anopheles stephensi*) and the most pathogenic species of parasite (*P. falciparum*). These challenges are exacerbated in low-income settings and/or conflict-prone areas, which create vulnerability through limited public resources and weaker health systems.

The Covid-19 crisis disrupted the delivery of malaria services, because of lockdowns and the repurposing towards Covid-19 of malaria funding, health system capacities and commodity production capacities[7]. Recovery from Covid-related reversals has increased need[8]. Now, the multiplication of extreme weather events and the impact of climate change is altering the dynamics of the pandemic, changing the

[3] WHO's list of dates that countries have achieved elimination. Available at : https://www.who.int/teams/global-malaria-programme/elimination/countries-and-territories-certified-malaria-free-by-who
[4] Bhatt S. et al. The effect of malaria control on Plasmodium falciparum in Africa between 2000 and 2015. Nature. 2015 Oct 8;526(7572):207-211. doi: 10.1038/nature15535. Epub 2015 Sep 16. PMID: 26375008; PMCID: PMC4820050.
[5] Unicef Data Website. Available from: https://data.unicef.org/topic/child-health/malaria/
[6] WHO World Malaria Report 2023
[7] Impact on reduced production of malaria rapid diagnostic tests noted in Unitaid's Malaria diagnostics market and technology landscape (2022).
[8] WHO World Malaria Report 2023

geographical distribution of malaria as well as its seasonal patterns, and causing extreme resurgence in flooded areas such as in Pakistan in 2023. Finally, demographic trends contribute a further stress upon existing resources. The population of under 5 children in Africa grew by nearly 50% between 2000 and 2020, it is expected to grow a further 25% between now and 2040.[9]

As experts of the Lancet commission on malaria eradication[10] and the WHO's Strategic Advisory Group on Malaria Eradication[11] have warned, reaching the target set in objective 3.3 of the Sustainable Development Goals of reducing malaria incidence and mortality rates by 90% by 2030[12] will require more time to be met (i.e. beyond 2030) if funding – both international and domestic – doesn't increase drastically.

In this challenging and evolving context, the development and large-scale production of the first ever anti-parasitic vaccine represents both a major scientific success, and an opportunity to save many more lives among children under five in moderate- to high-transmission countries if rolled out alongside other existing tools in an integrated manner. However, malaria vaccines alone cannot replace other malaria tools and innovations, nor put the international community back on track towards the SDG target.

1. Vaccines efficacy

1.1. Efficacy documented in trials

Both vaccines recommended by WHO have undergone phase 3 trials[13] – i.e. randomized controlled efficacy[14] trials against placebo vaccination. RTS,S also underwent a pilot large-scale roll out of RTS,S in Ghana, Malawi and Kenya (Malaria Vaccine Implementation Program, led by WHO and co-funded by the Global Fund, Unitaid and Gavi), which provided evidence on the effectiveness of RTS,S in conditions resembling a real-world public health intervention. R21 has not yet undergone a large-scale implementation pilot project.

Studies indicate that the vaccines provide a significant temporary boost of protective immunity that reduces the number of clinical cases at a period when children are especially vulnerable to severe malaria and mortality, with impact varying across the age groups and study sites evaluated. Neither of the two vaccines is fully protective against infection, severe morbidity, or mortality; moreover, the immunity boost wanes over time.

As a prophylactic intervention, the vaccines alone are not better than the existing tool of seasonal malaria chemoprevention, which involves the monthly administration of 3 once-a-day medicines during peak malaria season; however, when introduced together, malaria vaccines and SMC showed a significant added value to the package of malaria interventions.

No malaria vaccine versus placebo vaccine study to date has been able to demonstrate a significant impact on malaria-related mortality.

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[9] According to the 2023 World Malaria Report, estimates of the malaria burden in African in 2000 were: 209 million cases, 808 thousand deaths; in 2022, the estimates were 233 million cases and 580 thousand deaths.

[10] Available from: https://www.thelancet.com/commissions/malaria-eradication

[11] WHO's Strategic Advisory Group on Malaria Eradication report on Malaria eradication: benefits, future scenarios & feasibility. Available from: https://www.who.int/publications/i/item/9789240003675

[12] SDG 3.3 also aimed to eliminate malaria in 35 countries and to prevent a resurgence in countries that had already achieved elimination.

[13] Phase 3 trials aim to evaluate efficacy of an intervention and to further monitor/validate safety data. Phase 3 trial data are submitted to regulatory authorities and serve as the key basis for regulatory approval of an intervention.

[14] A 45% vaccine efficacy does not mean 45% of vaccinated persons will not get malaria in the period, it means there will be a 45% reduction in malaria episodes among vaccinated persons.

1.1.1. RTS,S efficacy trial[15]

Over the two years following the first dose, a 32.2% (95% CI of 13·7 to 46·9) vaccine efficacy against severe cases of malaria was observed in the 5-17 month group receiving 3 RTS,S doses plus a booster dose; a slightly higher vaccine efficacy against clinical malaria (i.e. including both severe and non-severe cases) of 36·3% (95% CI 31·8–40·5) was observed. An estimated 1774 clinical malaria cases were averted per 1000 children vaccinated with four RTS,S doses over the four years of follow-up in the Phase 3 trial. No statistically significant impact of the RTS,S vaccine on severe malaria was observed in the study cohort aged 6-12 weeks in the 48-month window of evaluation.[16]

1.1.2. RTS,S effectiveness evaluation

RTS,S effectiveness data to date comes from the Malaria Vaccine Implementation Program, a large-scale, WHO-coordinated pilot program of RTS,S vaccination of nearly 2 million children across three countries.[17] Data publicly shared to date noted that the eligible cohort in vaccinated districts versus non-vaccinated districts experienced a 22% decline in hospitalizations from severe malaria, a 17% reduction in hospitalizations with a positive malaria test, and a 13% decline all-cause mortality.[18,19] However, it remains unclear how much of the all-cause decline in mortality may be attributable to a reduction in malaria-related mortality[20]; the pilot program did include malaria mortality as an endpoint to be measured, but the data has not been publicly reported yet.[21] In the absence of robust data demonstrating a decline in malaria-related mortality, the decline in all-cause mortality should not be interpreted to demonstrate the vaccine's impact on mortality.

1.1.3. R21 Efficacy Trial[22]

There is currently far less robust efficacy data for the second vaccine, R21. The R21 phase 3 cohort was 1/3 the size of the RTS,S phase 3 trial; moreover, whereas RST results reflecting outcomes over 48

[15] Tinto H et al. Long-term incidence of severe malaria following RTS,S/AS01 vaccination in children and infants in Africa: an open-label 3-year extension study of a phase 3 randomised controlled trial. Lancet Infect Dis. 2019 Aug;19(8):821-832. doi: 10.1016/S1473-3099(19)30300-7. Epub 2019 Jul 9. PMID: 31300331.

[16] RTS,S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. Lancet. 2015 Jul 4;386(9988):31-45. doi: 10.1016/S0140-6736(15)60721-8. Epub 2015 Apr 23. Erratum in: Lancet. 2015 Jul 4;386(9988):30. PMID: 25913272; PMCID: PMC5626001.

[17] Implementing countries were Ghana, Kenya, and Malawi between 2019 and 2023. In these countries, a set of districts were selected to be randomized as a district participating as an accelerated implementation district (i.e. the intervention arm where vaccinations were made available) or a delayed implementation district (i.e. the control arm). The participating cohorts were defined as an identical age band in both intervention and control districts; the evaluation (through surveys and surveillance) measured outcome in the whole eligible cohort (i.e. in the intervention arm, results for all those age-eligible to participate in the pilot were calculate, not only results for those in intervention districts who were vaccinated)

[18] Malaria Policy Advisory Group Day 1 presentations. October 2023. Available from: https://cdn.who.int/media/docs/default-source/malaria/mpac-documentation/mpag-documentation-day-1-october-2023.pdf?sfvrsn=1fadd469_3&download=true

[19] WHO. Full Evidence Report on the RTS,S.AS01 Malaria Vaccine. SAGE meeting October 2021. Available from: https://cdn.who.int/media/docs/default-source/immunization/mvip/full-evidence-report-on-the-rtss-as01-malaria-vaccine-for-sage-mpag-(sept2021).pdf

[20] Björkman A, Benn CS, Aaby P, Schapira A. RTS,S/AS01 malaria vaccine-proven safe and effective? Lancet Infect Dis. 2023 Aug;23(8):e318-e322. doi: 10.1016/S1473-3099(23)00126-3. Epub 2023 Apr 20. PMID: 37086747. Available from : https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(23)00126-3/abstract?fbclid=IwAR1bIj3UUx0x3nRmSIQm3POcqp2Mzu0Wn1ar-yvMGwSgTfu7xxLhG6Kh2C8

[21] Malaria mortality data was collected at sentinel hospitals, while all-cause mortality data was collected via verbal autopsies collected by resident village reporters.

[22] Datoo et al; R21/Matrix-M Phase 3 Trial Group. Safety and efficacy of malaria vaccine candidate R21/Matrix-M in African children: a multicentre, double-blind, randomised, phase 3 trial. Lancet. 2024 Feb 10;403(10426):533-544. doi: 10.1016/S0140-6736(23)02511-4. Epub 2024 Feb 1. PMID: 38310910.

months are available, the R21 data to date only captures the 12-18 months immediately after the first three doses of vaccination—the window where the greatest efficacy is expected. Having noted these asterisks, the R21 study observed a 72.4% vaccine efficacy (CI 69-75%) for clinical malaria in the study's 5–36-month cohort; a statistically significant smaller prevalence of asymptomatic malaria was also measured in the R21 arm. The trial was not powered to show a statistically significant impact on severe malaria or mortality. Moreover, over 1 in 3 trial participants benefitted from 4 or more rounds of SMC during the year evaluated, a parallel preventive intervention.[23] There is no real-world effectiveness data yet for R21; many countries plan to scale up R21 in 2024, including Nigeria—which accounts for one-fourth of malaria's global burden of disease.

1.1.4. Interpreting vaccine efficacy trials

Because of major differences in the parameters of the clinical trials of both vaccines, the phase 3 trials provide little basis for a strong head-to-head comparison of the two vaccines.[24] In its communication approving the R21 vaccine, the WHO declared that: "There is no evidence to date showing one vaccine performs better than the other. The choice of product to be used in a country should be based on programmatic characteristics, vaccine supply, and vaccine affordability."[25]

The absolute impact of the vaccine efficacy is shaped by the background transmission rate. For example, the R21 investigators noted that 868 clinical cases were averted per 1000 child years in seasonal settings versus 296 averted cases per 1000 child years in non-seasonal settings (over the evaluation period). While a very small portion of this gap is tied to a higher vaccine efficacy at seasonal versus non-seasonal sites (75% to 68%), the gap in average cases averted is primarily explained by the three times larger baseline incidence in sites with seasonal transmission versus incidence at non-seasonal sites (0.95 to 0.32 cases per child-year).

Moreover, it is important to emphasize the asterisk that the impact of the vaccines will also be shaped by the coverage and quality of malaria services in a given area. Where the most effective nets are made available and used, they offer significant protection and reduce the number of cases. Moreover, prompt diagnosis and treatment reduce the number of cases progressing to severe malaria. Finally, quality case management of severe cases can significantly impact mortality outcomes. The absolute and relative impact of the vaccine in a given setting may therefore depend on the local malaria response and its impact in reducing transmission, prompt diagnosis and treatment of cases, and effective management of severe malaria.

1.1.5. Cost-effectiveness

There is no evidence to suggest that the vaccines are more effective in reducing incidence and/or disease severity when vaccines alone are compared to existing preventive/prophylactic interventions. The efficacy/effectiveness of nets and SMC are highlighted in the table below. The costs of implementing interventions can vary from setting to setting; effectiveness can also vary according to the quality / coverage of implementation and evolving levels of resistance.

[23] 73% benefitted from at least one round of SMC.

[24] Given the lack of alignment of the phase 3 data available (including differing lengths of post-vaccination period examined to date), the unique cohorts (including the coverage of malaria interventions in those cohorts), and the unique combinations of trial site settings.

[25] WHO Website News Release. Available from: https://www.who.int/news/item/02-10-2023-who-recommends-r21-matrix-m-vaccine-for-malaria-prevention-in-updated-advice-on-immunization

A recent paper evaluated the cost-effectiveness of several malaria interventions across a wide range of cost/coverage/impact scenarios.[26] The analysis found that expansion of long-lasting insecticide-treated nets was consistently the most cost-effective malaria intervention, while the introduction of SMC and switching to new technology nets demonstrated superior cost-effectiveness to vaccines.[27]

The respective prices of commodities are a key factor driving the superior cost-effectiveness of nets and SMC over vaccines. At present, one highly-effective latest-generation net is only 20% the cost (in terms of commodity prices) of procuring 4 doses of the R21 vaccine and only 5% the cost of four doses of the RTS,S vaccine. Moreover, one net can offer protection lasting for up to three years and potentially provide protection to more than one person. In terms of pure commodity costs, seasonal malaria chemoprevention is significantly cheaper than vaccination, with four monthly courses per year over the course of four years equal to only 15% the costs of 4 doses of RTS,S and 40% the cost of R21.

Prompt diagnosis and treatment is essential to reducing the risk of cases progressing to severe malaria. The first line of treatment has a 98% efficacy and the commodities to test and treat uncomplicated malaria with that first line can cost less than one dollar. While the price of medicines for treating a case of severe malaria may only be 5-10 USD, hospitalization and treatment for severe anemia / cerebral malaria can balloon the costs.

With more data on vaccine effectiveness and operational costs, visibility should improve on cost-effectiveness of malaria vaccines across various settings. The cost-effectiveness of the vaccine will vary according to conditions in the local setting (feasibility of efficient alignment with routine immunization, incidence rates and seasonal patterns by geography, service delivery costs, etc). As a general observation, the cost-effectiveness of the vaccine will be greater in areas of high transmission. However, a boost in cost-effectiveness at higher transmission levels also applies to other protective interventions. Two key evolving factors will include changes in the price of vaccines and increased clarity on effectiveness of dose number / schedules (i.e. whether three primary doses are needed, and how great an impact the 4th and 5th doses may add). Beyond sub-Saharan Africa, cost-effectiveness of malaria vaccination at scale should vary as a function of *falciparum*'s percentage of the species profile in a given setting.

[26] Topazian HM, Schmit N, Gerard-Ursin I, Charles GD, Thompson H, Ghani AC, Winskill P. Modelling the relative cost-effectiveness of the RTS,S/AS01 malaria vaccine compared to investment in vector control or chemoprophylaxis. Vaccine. 2023 May 11;41(20):3215-3223. doi: 10.1016/j.vaccine.2023.04.011. Epub 2023 Apr 18. PMID: 37080831.

[27] The study assumes a price point of 9.30 USD. Even at prices of below 1 USD per dose, the vaccine is not judged to be the most cost-effective in most scenarios. The paper further notes: "From a purely cost-effectiveness perspective, our results show that the scale-up of existing interventions should be prioritized first in settings in which their benefits are not yet fully realized. However, in high transmission settings where existing interventions are being maintained at high coverage, RTS,S can have a substantial additional benefit in reducing malaria burden and morbidity at a cost-effectiveness level that is comparable to other recently introduced childhood vaccines."

Table 1: Overview of commodity prices and intervention efficacy / effectiveness

Intervention	Commodity prices (per pooled procurement via Wambo); does not include logistical / implementation costs	Mechanism of impact
Latest generation dual active ingredient insecticide nets (chlorfenapyr-pyrethroid) *Recommended to distribute a new net every three years*	2.56-2.94 USD per net *Each net can protect several individuals over 2+ years*	Reduces disease transmission and vector population. Insecticide-treated nets demonstrated roughly 50% reduction in clinical cases (versus no nets); in settings with pyrethroid resistance, the latest generation of dual active ingredient chlorfenapyr-pyrethroid nets reduced infections by 50%, when compared to pyrethroid-only nets.
Seasonal malaria chemoprevention (4 cycles) *Number of cycles per year and number of years of SMC depend on local conditions policy; season duration generally between 3-6 months*	1.12-1.56 USD per individual per year	Reduces symptomatic disease. A randomized clinical trial found SMC was non-inferior to RTS,S over the 3.5-year period of the study; a synthesis of case-control studies found SMC had an effectiveness of 73%-98% within 28 days of administration, 62% in the 4-6 week post-therapy window.
RTS,S Vaccine (4 doses) 9.3 EUR per dose	Approximately 40 USD per individual (four doses)	Reduces symptomatic disease. Significant reductions in clinical malaria (39%); severe malaria (29) demonstrated over 46 months.
R21 Vaccine (4 doses) 3.9 USD per dose	15.60 USD per individual (4 doses)	Reduces symptomatic disease. Reduction in symptomatic cases of malaria by 75% demonstrated over 12 months.
Diagnostic Rapid Test	0.28-0.65 USD per test	Reduces disease progression. Efficacy of 98% with recommended ACT in Africa.
Artemisinin -combination therapy (ACT)	0.28-0.65 USD per uncomplicated malaria case ; 5-10 USD per severe malaria case	

1.2. Gaps of knowledge on malaria vaccines efficacy

Ongoing and future research is needed to fill gaps in knowledge on RTS,S and R21 vaccine efficacy; research would also be needed to evaluate the efficacy of other vaccine candidates[28].

1.2.1. Attributable impact on mortality

RTS,S and R21 efficacy trials were not sufficiently powered to detect a mortality impact. While the MVIP RTS,S pilot evaluation data observed a 13% reduction in all-cause mortality in the vaccinated cohort and all-cause mortality is a robust finding, further data is needed to determine whether this decrease is

[28] Ongoing studies: MVIP has embedded a case-control study that will measure added benefit of 4th dose and will monitor for any rebound effect.

attributable to the vaccine. Data on malaria-related mortality during the MVIP has not yet been published.

1.2.2. Efficacy of fewer doses

None of the phase 3 studies evaluated the impact of a one- or two-dose primary series versus the full three-dose primary series. The question is relevant for two reasons: What vaccine efficacy can we expect for any children that are not completely vaccinated? Would a one- or two-dose primary vaccination approach yield significantly inferior vaccine efficacy?

1.2.3. Efficacy in settings and populations with low levels of exposure

The degree of exposure to the parasite—number of episodes of sporozoite infection—is generally associated with the development of immunity. In low-transmission settings where the rate of exposure is lower, high levels of vulnerability persist in older children (compared to the vulnerability at similar ages in moderate- and high-transmission levels). Populations with no lifetime (or limited recent) exposure to malaria may remain at risk, even as adults. This introduces two knowledge gaps: does the vaccine's impact on age groups vary according to the transmission setting? Would the vaccine have an impact in malaria-naïve adults in endemic settings?

1.2.4. Impact on transmission

The RTS,S and R21 vaccines aim to protect against the progression of sporozite infection of liver cells (the pre-erythrocitic stage); by targeting the sporozoite stage of the parasite life cycle, the vaccines directly aim to protect against the development / progression of symptoms.[29] Vaccines that aim to block transmission target a different form of the life cycle, known as gametocytes. Transmission-blocking vaccines have not yet reached phase 3 clinical trials. Even if proven effective in reducing transmission, these vaccines would not impact progression to disease of those infected, so the vaccine would not offer a direct benefit to the vaccinated.

1.3. Comparison with efficacy of other malaria tools

Malaria vaccines add value to existing core interventions. However, the vaccines do not offer value for money as a substitute for any of the core prevention or prophylactic interventions, as the vaccines are not superior in efficacy to existing preventive interventions and are by far more expensive. While vaccines can complement and even boost the impact of existing interventions, they should not replace them. The greatest added value of the vaccine will be in combination with the implementation of preventive measures, while prompt diagnosis and treatment will remain critical for "break-through" cases.

1.3.1. Efficacy of vector control

Insecticide-treated nets (ITNs) have long been a frontline of defence for malaria prevention targeting the mosquito vector, by providing a physical barrier to bites and a tool for killing mosquitos through the insecticide coating. The most recent comprehensive review of ITN effectiveness found a 17% reduction in all-cause child mortality and a nearly 50% reduction in uncomplicated episodes of malaria, when compared to no nets.[30] A study financed by the Global Fund demonstrated that in a setting with high

[29] There is not clear evidence that limiting the progression of sporozoites to disease (caused by merozoites) has any impact on malaria transmission (caused by gametocytes) is not conclusive. In the RTS pilot study, no impact was observed on incident rates of severe malaria cases in the cohorts of older children who, while not eligible for vaccination, had their outcomes tracked in both the intervention and control districts.

[30] Pryce J, Richardson M, Lengeler C. Insecticide-treated nets for preventing malaria. Cochrane Database Syst Rev. 2018 Nov 6;11(11):CD000363. doi: 10.1002/14651858.CD000363.pub3. PMID: 30398672; PMCID: PMC6418392.

pyrethroid resistance levels, the latest generation of dual-ingredient chlorfenapyr-pyrethroid long-lasting insecticide nets (LLITNs) reduced infections by 50%, when compared to pyrethroid-only LLITNs.[31] The year this study was ultimately published, the WHO made its first recommendation for the addition of two dual active ingredient nets to its guidelines. Given the added value of dual active-ingredient chlorfenapyr-pyrethroid nets in pyrethroid-resistant areas, it is important to note that the new-generation nets are only 25-50% more expensive than standard insecticide-treated nets. The Global Fund has helped catalyze the affordability of the new nets through their market-shaping interventions; moreover, Global Fund have accelerated scale up through their New Nets Project.[32]

1.3.2. Efficacy of parasite-targeting prophylactic interventions

Vaccines are not the only or even first prophylactic tool targeting the malaria parasite. Preventive chemotherapy is recommended for pregnant women (in malaria-endemic settings) and seasonal malaria chemotherapy for children (recommended by WHO for children under 5 in settings of intense seasonal transmission since 2012). A series of seven case-control studies on seasonal malaria chemoprevention (SMC) found an effectiveness of 73%-98% within 28 days of administration of a monthly dose in a cohort with an average age of roughly 2 years old; this protection was similar to the level observed in clinical trials for SMC efficacy.[33] The protection fell to 62% in the 4–6-week post-therapy window.

A robust randomized 5-year study examining RTS,S vaccination against and with SMC demonstrated that the vaccine was non-inferior to SMC alone: however, when RTS,S is used in combination with SMC, a massive added value was observed: a 60% reduction in clinical cases, 60% reduction in severe cases, and 40% reduction in all-cause mortality when compared to outcomes in the SMC or RTS,S arms alone.[34],[35],[36]

In terms of pure commodity prices, seasonal malaria chemoprevention over the course of four years (four months per year) is 15% the costs of 4 doses of RTS,S and 40% the cost of R21. This gap in costs would grow further if 5 vaccine doses are implemented.

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[31] Accrombessi M, Cook J, Dangbenon E, Yovogan B, Akpovi H, Sovi A, Adoha C, Assongba L, Sidick A, Akinro B, Ossè R, Tokponnon F, Aïkpon R, Ogouyemi-Hounto A, Padonou GG, Kleinschmidt I, Messenger LA, Rowland M, Ngufor C, Protopopoff N, Akogbeto MC. Efficacy of pyriproxyfen-pyrethroid long-lasting insecticidal nets (LLINs) and chlorfenapyr-pyrethroid LLINs compared with pyrethroid-only LLINs for malaria control in Benin: a cluster-randomised, superiority trial. Lancet. 2023 Feb 11;401(10375):435-446. doi: 10.1016/S0140-6736(22)02319-4. Epub 2023 Jan 24. PMID: 36706778.

[32] Available from: https://unitaid.org/news-blog/global-fund-and-unitaid-welcome-who-recommendation-for-insecticide-treated-nets-with-dual-active-ingredients/#en

[33] Cairns M, Ceesay SJ, Sagara I, Zongo I, Kessely H, Gamougam K, Diallo A, Ogboi JS, Moroso D, Van Hulle S, Eloike T, Snell P, Scott S, Merle C, Bojang K, Ouedraogo JB, Dicko A, Ndiaye JL, Milligan P. Effectiveness of seasonal malaria chemoprevention (SMC) treatments when SMC is implemented at scale: Case-control studies in 5 countries. PLoS Med. 2021 Sep 8;18(9):e1003727. doi: 10.1371/journal.pmed.1003727. PMID: 34495978; PMCID: PMC8457484.

[34] Chandramohan D, et al. Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention. N Engl J Med. 2021 Sep 9;385(11):1005-1017. doi: 10.1056/NEJMoa2026330. Epub 2021 Aug 25. PMID: 34432975.

[35] SMC is not recommended in non-seasonal settings, meaning that effectiveness presumably differs between seasonal and perennial transmission settings; important to understand relevance in both seasonality and transmission levels for cost-effectiveness. Moreover, a potential rebound effect in populations receiving a vaccine/SMC combination would be important to evaluate, given documented concerns over a rebound effect with SMC.

[36] Ndiaye M et al. Potential Impact of Seasonal Malaria Chemoprevention on the Acquisition of Antibodies Against Glutamate-Rich Protein and Apical Membrane Antigen 1 in Children Living in Southern Senegal. Am J Trop Med Hyg. 2015 Oct;93(4):798-800. doi: 10.4269/ajtmh.14-0808. Epub 2015 Aug 17. PMID: 26283746; PMCID: PMC4596602.

2. Malaria vaccines implementation

2.1. WHO guidance on vaccines roll out

WHO recommendations provide green lights and WHO guidelines provide roadmaps for policy implementation. The WHO's recommendations offer general indications on who, where and how to vaccinate, as well as on the role of vaccines in broader malaria strategies. However, an important void in detailed operational guidance remains because the WHO has not yet released a planned "Guide for introducing a malaria vaccines". WHO recommendations and guidelines on the malaria vaccines are likely to evolve in the coming years as both the evidence base and the supply base are poised to grow.

2.1.1. Who, where and when to vaccinate

At present, the WHO only recommends the introduction of the two malaria vaccines in moderate to high transmission settings, for children above 5 months old.[37],[38] The WHO recommendations leave some areas unclear, for example, the WHO does not set a clear upper age limit for vaccination[39], and does not propose a clear guidance on moderate to high transmission settings where *P. falciparum* is not the dominant species—i.e. settings outside of sub-Saharan Africa.

The recommended vaccination schedule indicates that the first three doses should be given with a minimum interval of four weeks between doses. A 4th booster dose should be administered 12-18 months after the 3rd dose, with the WHO noting that flexibility may be considered to align a 4th dose with vaccines administered in the second year of life and/or just before highly seasonal transmission / seasonal peaks.[40] The WHO notes that a 5th dose may be considered (also prior to peak season). In other words, the recommendations afford countries a wide range of flexibility in deciding when they carried out the primary series of vaccinations and the booster doses. The recommendations encourage countries to adopt their own implementation approach to an age-based (structuring malaria vaccination to align with timing of routine vaccination) or season-based vaccination schedule (scheduling primary and/or booster doses to occur before peak season). This flexibility is consistent with WHO's recommendation for other interventions, especially the timing and duration of seasonal malaria chemoprevention; the WHO encourages countries to adapt intervention rollout to local seasonality and intensity.

2.1.2. Integration

The WHO recommendation insists that the vaccine should be considered as an additional tool to include, along with existing tools and other innovations, as part of integrated malaria strategies.

Ideally, all eligible children would be able to access all malaria prevention, diagnostics, and treatment tools, and the roll out of the malaria vaccine through broader immunization platforms would boost existing tools to drastically reduce malaria cases and deaths. In a real-world context, rolling out the malaria vaccine through routine immunization platforms could potentially help reach children who are

[37] WHO Website. Available from: https://www.who.int/news/item/06-10-2021-who-recommends-groundbreaking-malaria-vaccine-for-children-at-risk (Accessed 24/1/24)

[38] The WHO defines moderate or high transmission settings as those with an annual incidence greater than about 250 cases per 1000 population or a prevalence of P. falciparum infection in children aged 2—10 years (PfPR2-10) of approximately 10% or more.

[39] Trial data and broader epidemiological data indicate that natural immunity progresses through childhood as a function of increasing exposure. This means that in areas with relatively higher rates of transmission, the development of natural immunity is believed to progress faster. Future studies may indicate whether these distinct trajectories of immunity—and vulnerability—lead to different vaccination strategies in different settings / populations.

[40] WHO guidelines for malaria, 16 October 2023. Geneva: World Health Organization; 2023 (WHO/UCN/GMP/ 2023.01 Rev.1). License: CC BY-NC-SA 3.0 IGO.

not covered, or only partly covered, by existing malaria preventive tools, and expand the number of children in moderate to high transmission settings who access at least one malaria prevention tool. In fact, in the MVIP pilot of the RTS,S vaccine, survey results from the Ghana cohort indicated that 39% of the eligible population (12-23 months) were not using LLITNs. Among the population not using LLITNs, vaccine coverage reached 84% of that population—i.e. 33% of the population was vaccinated but not sleeping under LLITNs. In the pilot setting, the evaluation data suggested that the introduction of the vaccine did not alter the use of other malaria prevention tools. It will be important to track how the introduction of the malaria vaccine may influence uptake of other interventions including malaria diagnosis and treatment, and to ensure correct communication messages about the limited protective effect of malaria vaccines, as communities' understanding and experiences about the package of interventions may shape the uptake of specific interventions.

There is also a strong case for coupling the delivery of nets with immunization – whether for malaria or for another disease. Immunization campaigns present an opportunity—at either routine immunization for malaria vaccination or other vaccines—to distribute additional nets to children/caregivers when children are presenting for vaccination. In fact, distribution of nets at antenatal care and immunization services is a long-standing recommendation.[41] WHO has noted that the distribution of long-lasting insecticide nets have been successfully integrated into infant and child immunization, a point backed by several successful examples from the literature.[42],[43],[44]

2.1.3. Prioritization

In settings with limited resources and health system capacities, policymakers must evaluate how to prioritize and optimize efforts across the package of possible malaria interventions. In support of this process, WHO often plays a key role through its synthesis of global evidence of cost-effectiveness of new interventions and service delivery approaches; syntheses of cost-effectiveness studies are used to inform WHO recommendations and to support country-level decision processes. While the WHO's recommendations avoid setting a clear hierarchy across interventions, they do emphasize that local prioritization should be carried out and that analyses by local decision-makers should aim to integrate cost-effectiveness considerations. This includes sub-national prioritization, including for the vaccine, meaning that different delivery models may coexist in a single country.

The WHO recommendations do not declare a clear position on the relative prioritization of vector control, versus prophylaxis such as preventive chemotherapy and/or vaccines, versus prompt diagnosis and treatment. However, the WHO Malaria Policy Advisory Group (MPAG)—an independent advisory group of experts that provides strategic advice and technical input to WHO—recently issued a far more direct position in late 2023 (i.e. following their review of the R21 phase 3 trial data and the RTS,S pilot study data). According to MPAG, vector control and treatment of malaria cases should be the first priority, noting in its November 2023 paper titled Guiding Principles for Prioritizing Malaria Interventions: "New chemoprevention strategies should not be prioritized over and above case

[41] WHO Recommendations to Reach Universal Coverage with long-lasting insecticidal nets. March 2014. Available from: https://www.afro.who.int/sites/default/files/2017-06/who_recommendations_universal_coverage_llins.pdf

[42] Mathanga DP, Luman ET, Campbell CH, Silwimba C, Malenga G. Integration of insecticide-treated net distribution into routine immunization services in Malawi: a pilot study. Trop Med Int Health. 2009 Jul;14(7):792-801. doi: 10.1111/j.1365-3156.2009.02295.x. Epub 2009 May 26. PMID: 19497078.

[43] Grabowsky M, Farrell N, Hawley W, Chimumbwa J, Hoyer S, Wolkon A, Selanikio J. Integrating insecticide-treated bednets into a measles vaccination campaign achieves high, rapid and equitable coverage with direct and voucher-based methods. Trop Med Int Health. 2005 Nov;10(11):1151-60. doi: 10.1111/j.1365-3156.2005.01502.x. PMID: 16262740.

[44] A desk review was not able to immediately identify (a) a report documenting the extent that Global Fund resources supported procurement / distribution of nets during routine immunization; (b) a broader survey of the practice of net distribution by immunization programs.

management and vector control (insecticide-treated nets or indoor residual spraying) in any given population."[45] Timely diagnosis and treatment is critical to reducing the severity of cases and mortality. The MPAG advised that "scaling back access to early diagnosis and treatment is not an option under any level of financial constraint."[46]

The existing supply limitations will have an impact on country-level rollout. The WHO allocation framework has encouraged countries to create a hierarchy of zones (based primarily on transmission levels) to be prioritized for vaccination campaigns.

2.2. Anticipated obstacles in malaria vaccines roll-out

2.2.1. General obstacles

Nearly 25 million children are born annually in settings of moderate to high transmission of *P. falciparum*—a number which translates to 100 million doses (4 doses) or 125 million (5 doses). Gavi has estimated that 40-60 million doses will be needed annually by 2026, with 80-100 million doses needed by 2030.[47] It is reasonable to anticipate that the roll-out of malaria vaccines will face some of the same obstacles that contribute to existing gaps in access to existing tools – including insufficient levels for overall funding for anti-malaria programmes, insufficient health system capacities, and additional barriers to the deployment of malaria and primary healthcare services in rural areas, in conflict zones, and among the displaced.

Volume constraints may contribute to some of the existing gaps in recommendations and in research. The fact that the recommendations do not include under-five children in endemic-but-low-transmission settings may be explained partly by cost-effectiveness considerations; however, the near-term limitations in vaccine supply may also play a role in narrowing the settings/population targeted for rollout so long as supplies are limited. For similar reasons, the absence of research on the impact of the vaccine in older populations may be explained by the fact that studies on under-five children have been prioritized due to the hypothesis that the intervention will yield the greatest public health impact in this population. In other words, while there may be a gap in robust evidence about the impact of vaccination of children in low-transmission settings and the impact of vaccination in older populations, medium-term supply constraints may be influencing the priority given to filling such gaps.

2.2.2. Vaccines-specific obstacles

Tools cannot be delivered to populations without systems. System-level challenges differ depending on the type of tool. For early diagnosis and treatment, the challenge is to ensure that people with acute febrile illnesses access care and get diagnosed early and treated, whether they have malaria or another acute febrile illness. However, for multi-dose vaccines – as well as for multi-dose prophylaxy or treatment – the challenge is to make sure that children access the 3 to 4 doses they need at monthly intervals. Another key health system consideration for vaccination campaigns is that both vaccines require storage at 2-8 degrees Celsius, thereby requiring a minimum cold chain capacity to complement the interventions, as well as careful management of stocks to avoid expiration of commodities.

[45] WHO Website, Synthesis of Documents MPAG Meeting from 1 October 2023. Available from: https://cdn.who.int/media/docs/default-source/malaria/mpac-documentation/mpag-documentation-day-1-october-2023.pdf?sfvrsn=1fadd469_3&download=true (Accessed 24/1/24)
[46] WHO Website, MPAG Meeting Synthesis. Available from: https://cdn.who.int/media/docs/default-source/malaria/mpac-documentation/mpag-documentation-day-1-october-2023.pdf?sfvrsn=1fadd469_3&download=true (Accessed 24/1/24)
[47] Gavi Website. Available from: https://www.gavi.org/news/media-room/gavi-outlines-plans-build-sustainable-supply-malaria-vaccines (Accessed 24/1/24)

In the vaccines space, trust, uptake and compliance among communities are particularly challenging factors that determine the final impact of public health immunization policies. The impact of these dynamics may vary by local setting. While the current gap in malaria vaccination is due to the novelty / limited supply of the vaccine, the MVIP RTS,S pilot evaluation provided some preliminary data on uptake: a coverage of 64-74% was observed for the primary series in the districts where the vaccine was offered; however, a coverage of less than 50% was observed for the 4th dose.

Ensuring correct understanding of the vaccine among communities may also be expected to be a difficult challenge. The major difference of efficacy between malaria vaccines and other vaccines such as measles (98% efficacy) may lead to false representations among communities on the risk for vaccinated children to experience clinical or severe malaria episodes – which could have a counterproductive effect on mortality. The coexistence of different delivery patterns in a same country – depending for example on seasonal or continued transmission patterns-- could be an important challenge, in terms of ensuring that prevention messages are adequately differentiated.

2.3. Gaps that existing malaria vaccines cannot plug

2.3.1. Pregnant women, fetuses, and newborns

Nor RTS,S neither R21 are recommended for pregnant women. Pregnant women, given that malaria may account for between 10-20% of maternal mortality in malaria-endemic settings and malaria is associated with a 3-4 times increase in stillbirths, are a priority population. Children exposed to malaria during pregnancy are also at higher risk of growth retardation and future chronic diseases. In sub-Saharan Africa, over 2010-2022, although 78% of pregnant women had attended at least one prenatal consultation in a healthcare centre, only 42% had received the three recommended doses of prophylactic treatment. The development of a vaccine could help compensate for this gap. However, there are additional, gender-specific barriers to the development of new tools and technologies for pregnant women. A common gender bias, which has been documented[48],[49], is the absence of trials in pregnant women—or delays in conducting them.

The RTS,S phase III trial did include a cohort of 6-12 weeks but efficacy data was not sufficient for the WHO to include malaria vaccination at this early phase of infancy (i.e. before five months).

2.3.2. Access to early diagnosis and treatment

Major gaps exist in access to diagnostics and treatment. In 2022, only 30% of febrile children were tested for malaria in sub-Saharan Africa; only 23% of febrile children were tested for malaria in the West and Central African region; and only 56% of under 5 children with malaria are treated with the recommended artemisinin[50]-based combination therapy across sub-Saharan Africa; in the West and Central Africa region, that number falls to 44% (all data points are for 2022).

2.3.3. Access to other prevention tools

Vaccines alone are insufficient to prevent all malaria cases, but their efficacy is significantly higher when coupled with other prevention tools. SMC was scaled up from 170 thousand children in 2012 to 49

[48] Waitt, C., Astill, D., Zavala, E. et al. Clinical trials and pregnancy. Commun Med 2, 132 (2022). https://doi.org/10.1038/s43856-022-00198-1. Available from : https://www.nature.com/articles/s43856-022-00198-1
[49] Achieving a double dividend: the case for investing in a gendered approach to the fight again malaria. RBM Report. 2021. Available from: https://www.malarianomore.org/wp-content/uploads/2021/06/Malaria-and-Gender-Report_FINAL3.pdf
[50] Unicef Malaria Data. Available from : https://data.unicef.org/topic/child-health/malaria/

million children covered annually by 2022[51]; in a study evaluating uptake in eight countries in 2022, at least 90% received at least one cycle of SMC—with Nigeria reaching 90% coverage in settings where 4 cycles were being implemented.[52] However, important gaps in access to SMC remain. In the R21 efficacy trial, approximately a quarter of participants were not eligible for SMC, presumably because of a non-seasonal pattern, or of the absence of an SMC policy in their setting. The rest of the participants had at least one round, while 36% had 4 or more rounds. Over that same 2012-2022 period, the percentage of under 5 children sleeping under nets in sub-Saharan Africa grew from 38 to 58% – which still leaves a blatant gap, also considering that only 9% of nets distributed in 2022 were the new-generation, dual-ingredient nets that are most efficient against vector resistance to insecticide.

2.4. Shifts in the malaria pandemic that vaccines alone cannot address

2.4.1. Antimicrobial, diagnosis, and insecticide resistance

Resistance to pyrethroid, the long-standing go-to active ingredient for insecticide treatment of nets, is a major issue in sub-Saharan Africa. [53] Due to their limited efficacy, vaccines can only partly compensate for loss of efficacy of single-ingredient nets due to vector resistance. Dual-ingredien nets are most able to compensate for this. As the role of the use of pesticides in agriculture is a major driver of insecticide resistance, a One Health approach would be also needed to prevent its further expansion.

HRP2 gene deletions (and to a lesser extent, HRP3 deletions) threaten to undermine the ability of existing rapid diagnostics to detect malaria. At present, the high levels of HRP2 deletion seen in other regions, particularly Latin America, are not yet as common in Africa (based on studies to date)[54]. By reducing the number of clinical cases of malaria, the vaccine would not resolve this threat to effective case management; however, it could help reduce its impact by reducing the burden of cases.[55] Artemisinin resistance remains a greater threat in Asia's Mekong Delta; to date, there is no evidence of widespread Artemisinin resistance in sub-Saharan Africa –a situation that the spread of invasive species of mosquito *An. Stephensi* could alter.

2.4.2. Vector evolution

Several evolutions in the vector may further shift or even increase the intensity of malaria transmission. For example, some mosquitoes faced with insecticide-treated nets adapt their behavior, biting more outside and more during daytime, thereby reducing (but not eliminating) the value added of the physical barrier and vector-killing impact offered by the use of ITNs.The expansion of *Anopheles stephensi* in Africa is another major risk, as studies have demonstrated a correlation between *An. Stephensi* and malaria outbreaks in urban areas, as well as a correlation between *An. Stephensi* prevalence and spread of diagnostics- and drug-resistance in *P. falciparum*[56]. This mosquito species has demonstrated capacity to adapt to surviving extremely high temperatures during the dry season, when malaria transmission usually reaches a seasonal low. Native to South Asia and the Arabian Peninsula, the WHO has received reports of *An. Stephensi* having been detected in Djibouti, Eritrea, Ethiopia, Ghana, Kenya, Nigeria,

[51] World Malaria Report 2023

[52] Malaria Consortium. Coverage and quality of seasonal malaria chemoprevention supported by Malaria Consortium in 2022: Results from Burkina Faso, Chad, Mozambique, Nigeria, South Sudan, Togo and Uganda. April 2023.

[53] Malaria Threats Map.

[54] The majority of the RDTs used to detect *P. falciparum* malaria target the histidine-rich protein 2 (HRP2) antigen; therefore, the appearance of *P. falciparum* parasites that do not express HRP2 are a cause of concern, as they may escape detection by RDTs that are based on detection of HRP2.

[55] World Malaria Report 2023

[56] Emiru, T., Getachew, D., Murphy, M. *et al.* Evidence for a role of *Anopheles stephensi* in the spread of drug- and diagnosis-resistant malaria in Africa. *Nat Med* **29**, 3203–3211 (2023). https://doi.org/10.1038/s41591-023-02641-9 Available from: https://www.nature.com/articles/s41591-023-02641-9

Somalia, Sri Lanka, Sudan, and Yemen; most reports of the expansion of *An. stephensi* as an invasive species are in the northeast of Africa.

2.4.3. Climate change

WHO emphasizes that the direction of the effect of climate change on malaria transmission and burden will be non-linear and is likely to vary across different contexts, with key factors including variations in temperature, rainfall, or humidity. In the absence of sufficient data for modelling the impact of climate change on the vector, adaptation of malaria programmes to shifts in the distribution of malaria transmission is a challenge. Extreme weather events such as floodings may cause a massive surge in incidence by changing the intensity of transmission. This point was demonstrated recently by flooding in Pakistan, which experienced a significant surge in malaria cases and a major disruption in immunization programs.[57] Climate change may also alter seasons and make it therefore more difficult to plan for seasonal prevention campaigns – whether seasonal chemoprevention or seasonal immunization, although the longer-lasting protective effect of vaccines compared with chemoprevention may increase the relative value of malaria vaccines in seasonal transmission settings. Finally, the need to adapt health systems to climate change is likely to increase the cost of all health service delivery.

2.5. Further R&D and innovation needs

Social science studies will be needed to document the acceptability of existing vaccines and to identify the best delivery models and prevention messages for their roll out.

Considering the efficacy limitations of currently available malaria vaccines, and based on macro-trends in the malaria pandemic, the WHO's World Malaria Report noted the following areas as priorities for innovation: highly efficacious vaccines, longer lasting insecticides (preferably non-pyrethroid), vector control tools that address outdoor biting, efficacious single-dose preventive therapies (e.g. monoclonal antibodies), diagnostic tools that can detect latent stages of *P. vivax* infections, new antimalarial drugs to mitigate ACT resistance for treatment of disease, and single-dose chemoprevention therapies. Also essential are innovations in service delivery, surveillance, and analytics. The WHO's World Malaria Report notes that 603 million USD was spent on malaria R&D in 2022—over 200 million USD short of the 2021-2030 target of an annual spending of 851 million USD.

The addition of vaccines to the package of malaria interventions introduces two important areas for implementation research: 1) an evaluation of how to maximize efficiency and coverage of immunization; 2) an evaluation of the impact that malaria vaccine uptake may have on the uptake of complementary malaria interventions. This includes studies on knowledge, values, preferences, and experiences of communities.

One Health approaches to fighting malaria could also be explored in greater depth, as studies have suggested that interventions in areas of ecological risk factors may represent cost-effective interventions to reduce malaria transmission, even in the absence of malaria warning systems[58]. Other

[57] Health Policy Watch. Pakistan Races to Catch Up on Childhood Vaccinations After Floods. Available from: https://healthpolicy-watch.news/pakistan-races-to-catch-up-on-childhood-vaccinations-after-floods/#:~:text=The%20floods%20severely%20damaged%20health,seen%20by%20Health%20Policy%20Watch.

[58] Ernst KC, Adoka SO, Kowuor DO, Wilson ML, John CC. Malaria hotspot areas in a highland Kenya site are consistent in epidemic and non-epidemic years and are associated with ecological factors. Malar J. 2006 Sep 13;5:78. doi: 10.1186/1475-2875-5-78. PMID: 16970824; PMCID: PMC1586014. Available from : https://malariajournal.biomedcentral.com/articles/10.1186/1475-2875-5-78

approaches, such as ivermectin administration to livestock, could be further considered as well.[59] Alternatively, certain agricultural practices may be exacerbating insecticide resistance and therefore represent an important One Health dynamic shaping vector control efforts.[60]

3. Macro structures of vaccine roll out

3.1. Market dynamics

3.1.1. Prices

The RTS,S vaccine has been priced at 9.30 euros per dose (approximately 10 USD). The price of the R21 vaccine is currently set at a ceiling of 3.90 USD per dose. The R21 producer, Serum Institute of India, has committed to eventually offering a price of under 3 USD. The recommendation of new vaccine candidates, currently under phase 1 or phase 2 trial, may trigger additional competition in a highly oligopolistic market, and hopefully drive down prices. However, it is unlikely for any new vaccine to be recommended in the next 10 years, as no additional vaccine candidate has yet entered phase 3 clinical trials.

3.1.2. Volumes

Nearly 25 million children are born annually in settings of moderate to high transmission of *P. falciparum*—a number which translates to 100 million doses (4 doses) or 125 million (5 doses). The estimation of volumes needed might evolve in the coming years, as studies may indicate that fewer primary doses are needed and/or that more booster doses are ideal.

Gavi has estimated that 40-60 million doses will be needed annually by 2026, with 80-100 million doses needed by 2030.[61] Given the near-term shortage, and the need to allocate scarce supply until the volume available expands to meet the need/demand, a framework for allocation was developed though a WHO-led adviser working group in combination with a WHO-led consultation process; its principles are greatest need, maximize health impact, equity, fair benefit sharing, and a cap on the volume of doses allocated to a single country. A notable absentee from the list of countries to receive RTS,S doses from Gavi is Nigeria,[62] a country that accounts for a quarter of the global malaria burden and double the burden of DRC, the country with the second highest burden. Gavi/Unicef have bought 18 million doses of RTS,S for the 2023-2025 period (4-6-8 million manufactured in 2023, 2024, and 2025 respectively); this appears to represent the full production capacity of GSK through the end of 2025. GSK has indicated that it plans to produce 15 million doses annually from 2026-2028.[63]

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[59] Landier J, Rebaudet S, Piarroux R, Gaudart J. Spatiotemporal analysis of malaria for new sustainable control strategies. BMC Med. 2018 Dec 4;16(1):226. doi: 10.1186/s12916-018-1224-2. PMID: 30509258; PMCID: PMC6278049. Available from: https://malariajournal.biomedcentral.com/articles/10.1186/s12936-015-1001-z

[60] Urio NH et al. Effects of agricultural pesticides on the susceptibility and fitness of malaria vectors in rural south-eastern Tanzania. Parasit Vectors. 2022 Jun 16;15(1):213. doi: 10.1186/s13071-022-05318-3. PMID: 35710443; PMCID: PMC9204902.

[61] Gavi Website. Available from: https://www.gavi.org/news/media-room/gavi-outlines-plans-build-sustainable-supply-malaria-vaccines (Accessed 24/1/24)

[62] The absence is apparently due to Nigeria's failure to apply for support from Gavi to access Gavi's RTS vaccine supply. It is possible (though unconfirmed) that the reason Nigeria has not applied is that Nigeria plans to scale up R21 rollout, as it has approved R21 and it had previously announced a broader partnership with SII.

[63] The flexibility to greatly expand supply of RTS is potentially undermined by the fact that the vaccine's AS01 adjuvant, which is an essential ingredient of the vaccine, is extracted from the Soapbox tree. The adjuvant is also used in GSK's blockbuster shingles vaccine (Shingrix); the AS01 adjuvant is also an essential component of a promising TB vaccine candidate that is currently undergoing phase 3 trials. The ability to overcome this potential bottleneck of natural supply may depend on success in developing a synthetic version of the adjuvant.

In contrast, the Serum Institute of India's claims that it has the potential to develop an annual production capacity of 100-200 million doses; given the SII's track record as the largest vaccine producer in the world, this is a credible projection.[64]

3.1.3. The role of local/regional manufacturing

By the end of the decade, the number of producers of RTS,S and R21 could expand. GSK, Bharat Biotech of India (BBIL), and PATH announced in January 2021 the signing of a technology transfer agreement, a process which is expected to be completed by 2028. Though Bharat Biotech is expected to develop the capacity to produce a greater volume of antigens then GSK, Bharat Biotech will still depend on GSK for the adjuvant. While Bharat's entry would represent a second vaccine producer in the Global South, it would not necessarily constitute a boost to local/regional manufacturing because the adjuvant would have been developed elsewhere.

For those promoting local / regional manufacturing as an advance in supply sovereignty / security, the production of the antigen and adjuvant would be essential. It appears that SII may develop some production capacity in Ghana and Nigeria. Initial reports highlighted the breaking of ground on a fill-and-finish plant in Ghana; it is unclear if antigen or adjuvant capacity is also foreseen. SII announced in September 2022 a collaboration with a Nigerian public-private entity; promoted as tech transfer to establish manufacturing capacity, it is also unclear in the Nigerian case if this capacity would extend to production of the key antigens and adjuvants. [65]

Moreover, the impact these local initiatives would have on volume or price is not known. SII may be expanding production collaboration to Ghana and Nigeria, but it is not yet clear when that would be or how that will influence scale/price, nor how much of the production process would be localized (i.e. SII may not localize all steps of the process, such as production of the antigen or adjuvant).[66]

3.2. Malaria multilateral architecture

The WHO estimates that 9 billion USD in annual funding is needed for the malaria response, meaning the current annual spending of 4.2 billion USD falls far short of the target level of resources. The funding needed to roll out malaria vaccines come on top of that. Without increased resources, vaccine scale up will come at the expense of coverage of other malaria interventions. Whether vaccination will come from existing resources at the expense of access to other tools, or whether vaccination will boost the mobilization of additional resources in the overall malaria funding panorama, will need to be closely monitored as large-scale purchase of RTS,S and R21 supply continues.

3.2.1. Roles of multilateral funders: Global Fund, Gavi, and Unitaid

Among the 11 countries that account for 70% of the global malaria burden[67], six are low-income countries whose restricted fiscal space make it impossible for them to plug national malaria funding gaps

[64] Serum Institute of India Press Release from 2 October 2023. Available from : https://www.seruminstitute.com/press_release_sii_021023.php (Accessed 24/1/24)

[65] Similar questions of full supply sovereignty also apply to claim of local manufacture of medicines (key substance being the APIs and essential molecules for API production) and diagnostics (e.g. reagents for PCR, antibodies for RDTs).

[66] Adepoju P. "Africa to Manufacture New Malaria Vaccine." Health Policy Watch. April 24, 2023. Available at: https://healthpolicy-watch.news/africa-to-manufacture-new-malaria-vaccine/ (Accessed 24/1/24)

[67] Burkina Faso, Cameroon, the Democratic Republic of the Congo, Ghana, India, Mali, Mozambique, Niger, Nigeria, Uganda, and, Tanzania ; 2023 WHO World Malaria Report

with domestic resources. While all are eligible for Global Fund grants, one is not eligible for Gavi financial support and two are due to transition from Gavi support by 2032.

The Global Fund is the main international player in the global financial architecture for malaria. Its role is to support countries to deploy malaria diagnosis, treatments, and prevention at a very large scale. It also leverages domestic funding resources towards HIV, tuberculosis, malaria, and health systems. The Global Fund provides 65% of all international financing for malaria programs and has invested more than 17.9 billion USD in malaria control programs as of June 2023. In countries where the Global Fund invests, malaria deaths have dropped by 28% between 2002 and 2022. Without these interventions, malaria deaths would have increased by 90% over the same period.

Unitaid has been involved in the global fight against malaria since its creation in 2006. In complementarity and partnership with the Global Fund[68], Unitaid focuses on lifting barriers to the availability and affordability of malaria products and to the development of new intervention delivery models.

Gavi, the Vaccine Alliance, has just entered the global malaria space by initiating large-scale roll out of RTS,S vaccine in 12 African countries. Gavi's mandate and investments are limited to immunization; Gavi currently supports vaccination targeting 19 infectious diseases. The malaria vaccine represents Gavi's first significant programmatic intervention in one of the three diseases prioritized by the Global Fund. Although neither Global Fund nor Unitaid mandates cover vaccines, both organizations co-funded the MVIP pilot project alongside Gavi, which constituted the basis for the WHO recommendations and the large-scale roll out of RTS,S by Gavi. In November 2023, Gavi started supporting the large-scale roll-out of the 18 million doses of the RTS,S vaccine it has secured for 2023-2025, with a first phase including 12 African countries –six further countries have been approved for inclusion in Gavi's program (i.e. bringing the number included to 18), while 28 in total have expressed interest.[69] Moreover, Unicef, the key operational partner of Gavi, issued a tender for an order of 713 million USD of R21 doses in late 2023, a seemingly clear indication of the ambitions to scale up support of malaria vaccination campaigns.[70]

Global Fund, Gavi and Unitaid mandates and investments are complementary in many ways. All three organisations engage in diseases that represent the leading causes of the global burden of disease in children. Global Fund, Unitaid, and Gavi are also complementary in relation to important co-morbidities associated with HIV, tuberculosis, and malaria, such as HPV diagnostics and vaccines. Both Gavi and Global Fund are also major international funders of health systems in low- and middle-income countries, although from different perspectives. While health system needs for routine immunization partly differ from health systems needs for HIV, tuberculosis, and malaria programmes – for example in terms of supply chain and delivery models – their needs converge in certain areas, such as laboratory and surveillance capacities.

3.2.2. Roles of multilateral normative and technical partners: WHO and RBM Partnership to End Malaria

As the leading global normative health organisation, WHO's efforts are pivotal in shaping how malaria vaccines are integrated into the biomedical and operational research agendas on malaria interventions; in developing more detailed policy and programmatic guidance; and in supporting

[68] Unitaid website. Available from: https://unitaid.org/news-blog/partnership-report-unitaid-and-the-global-fund/
[69] Gavi has capped doses per country at 1 million and has approved 18 countries in total for receipt of vaccine doses.
[70] Development Aid website notice. Available from: https://www.developmentaid.org/organizations/awards/view/474561/malaria-vaccine-contract-2

countries to develop national strategic plans against malaria that are evidence-based, equitable, differentiated by local needs and capacities, and integrated into broader national health strategies. The RBM partnership to end malaria, in its convening and catalytic role, supports the quality and effectiveness of countries and regional programming, also in partnership with international partners, and the deployment and scale-up of new products, techniques, and implementation strategies. Both WHO and the RBM Partnership to End Malaria have a crucial role to play in tracking global progress and challenges against malaria, and in mobilizing political will in support of resource mobilization efforts of Global Fund, Unitaid, and Gavi, as well as of domestic resource mobilization.

CONCLUSION: Governments and communities of endemic countries on the frontline

Malaria-endemic countries and their communities are on the frontline of the global fight against malaria and keep paying a deadly toll for the disease. In the town of Houndé in Burkina Faso, malaria represents 87% of hospitalizations and 50% of deaths among children under five[71]: In similar high-transmission settings, the malaria burden still strains limited health system capacities – and other infectious and non-infectious diseases cannot be tackled without accelerated efforts to combat malaria. The floodings in Pakistan have also shown the fragility of the progress made against the disease, and how rapid and deadly malaria resurgence can be. The updated WHO malaria vaccine recommendations have triggered a renewed wave of attention, enthusiasm, and hope for the global fight against malaria among decision-makers, among public opinion, and in the global media. Yet, as malaria vaccines must be rolled out on top of existing malaria control and elimination interventions as well as R&D, they represent an additional need in an already hugely underfunded fight.

Five years away from the 2030 target of achieving 90% reduction of the global malaria burden, global funding constraints represent the main and urgent obstacle to be lifted. Over the past decade, domestic investments from endemic countries represented 31% of total malaria funding, amounting to 1.1 billion USD in 2020. In March 2024, health ministers from high-burden countries in Africa renewed their commitment to end malaria.[72] The optimization of available funding of malaria by decision-makers in endemic countries, is the other main lever to accelerate progress towards the 2030 target - and requires the active involvement of country-level stakeholders, with communities affected by malaria foremost among them.

In a context marked both by new tools and by high levels of external financial contributions, international financing and normative actors play a central role in equipping governments in endemic countries with the evidence, guidance, and leeway they need to reach the highest public health impact possible with available resources. 69% of global malaria investments coming from international funding, 65% of those investments coming from the Global Fund, and international funding for malaria vaccines coming almost entirely to date from Gavi. The success of the Global Fund and Gavi replenishments in 2024 and 2025 will determine the level of external funding available for malaria interventions in low- and middle-income endemic countries over the next 5 years. Global Fund and Gavi and policies will also determine the ability of endemic countries to invest strategically in national malaria programs of endemic countries and transform financial resources into the highest and most equitable possible public health outcomes.

Thanks to its unique model, Global Fund has demonstrated its ability to mobilize funding and to support countries in transforming those financial investments into public health outcomes, infections averted, and lives saved. It is essential to take stock of lessons learned through the Global Fund and to foster partnership, performance, transparency, and ownership among all governmental and non-governmental actors while deploying new malaria tools, with communities at the centre.

Looking toward 2030 and beyond, in countries with the most constrained fiscal space, it will not be possible to accelerate and sustain progress against malaria with national financial resources alone– in these settings, there can be no transition from external financial support mechanisms without elimination.

[71] Intervention of Mahamadou THERA on "Vaccin antipaludique RTS,S/AS01 en vaccination saisonnière au Mali", in a webinar on malaria vaccines organized by the French National Academy of Medicines, February 2024. Available from: https://www.academie-medecine.fr/7-fevrier-2024-webinaire-vaccins-antipaludiques/?lang=en

[72] WHO AFRO Website. Available from: https://www.who.int/news/item/06-03-2024-african-health-ministers-commit-to-end-malaria-deaths

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About Friends of the Global Fund Europe

Friends of the Global Fund Europe is a non-profit organization, active in France, Germany, Italy, Spain, Belgium, Luxembourg and with the European Union, and committed alongside the Global Fund to Fight AIDS, Tuberculosis and Malaria to promote the fight against these three major pandemics and more broadly global health in Europe. Created in 2005, our organization is governed by a Board of Directors composed of political and scientific personalities from different European States. We carry out political advocacy activities aimed at informing decision-makers and members of parliaments of the main European donor countries of the Global Fund of the challenges and results achieved in the field of the three pandemics and their potential effects on global health.