
Webinar 7: R21/Matrix-M malaria vaccine and implications to African NITAGs

NITAG Support Hub (NISH) - Vaccinology webinar series for
NITAGs in Africa

29 November 2023, 12:00-14:00 CAT

Mgaywa Magafu, Lindsey Wu, Rafiq Okine, Eliane Furrer
World Health Organization



Credit: WHO/F.Combrink



Webinar 7: R21/Matrix-M malaria vaccine and implications to African NITAGs

Update on Malaria Vaccines

- Progress on RTS,S/AS01 introduction in Africa - Mgaywa Magafu (10 min)
- R21/Matrix-M: Safety, efficacy, and impact data - Lindsey Wu (20 min)
- Updated WHO malaria vaccine recommendation - Rafiq Okine (10 min)
- Implications of R21 on malaria vaccine introduction in Africa – Eliane Furrer (10 min)

Progress on RTS,S/AS01 malaria vaccine introduction in Africa

Mgaywa Magafu, WHO AFRO

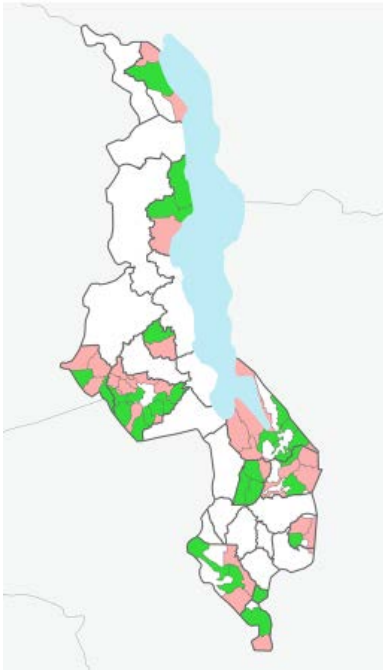
RTS,S/AS01 malaria vaccine implementation since 2019

Expanded to comparator areas since Nov 2022 – March 2023

Malawi

First introduced: 23 April 2019

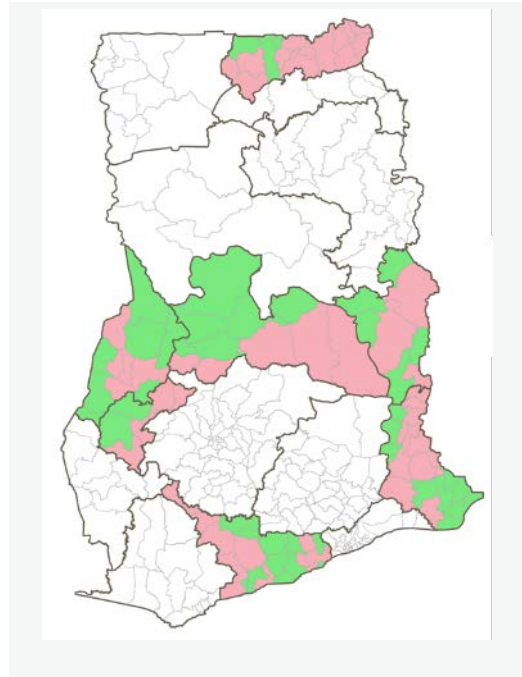
Expanded: 29 Nov 2022



Ghana

First introduced: 30 April 2019

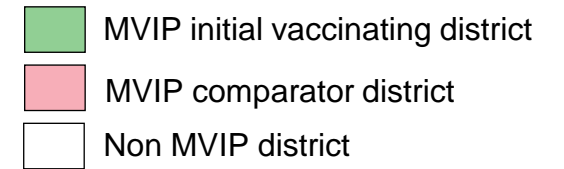
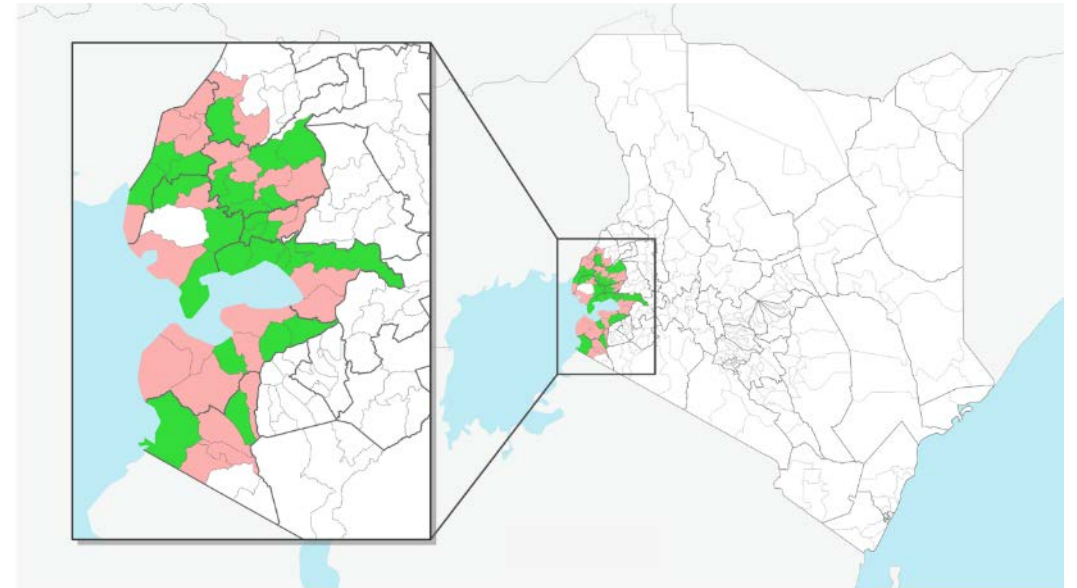
Expanded: 20 Feb 2023



Kenya

First introduced: 13 Sept 2019

Expanded: 7 March 2023



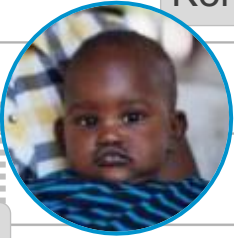
Malaria Vaccine Implementation Programme progressing well since 2019; MVIP end: December 2023

As of October 2023

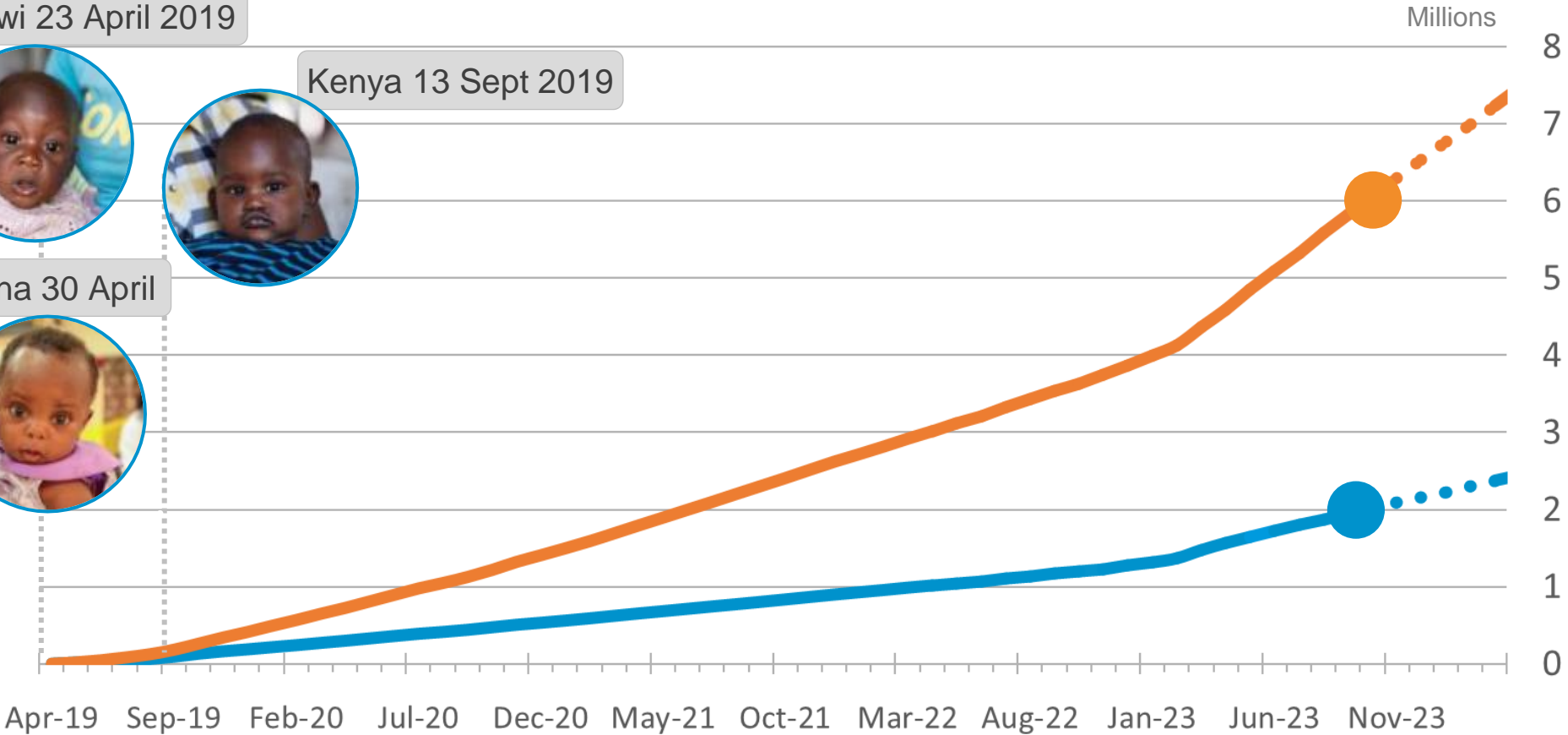
Malawi 23 April 2019



Kenya 13 Sept 2019



Ghana 30 April



> 6.0 million
vaccine doses
administered

> 2.0 million
children
received at least
one dose

Estimates as of October 2023 - based on monthly MOH/EPI administrative data reports until Aug 2023 and MVIP team projections for subsequent months

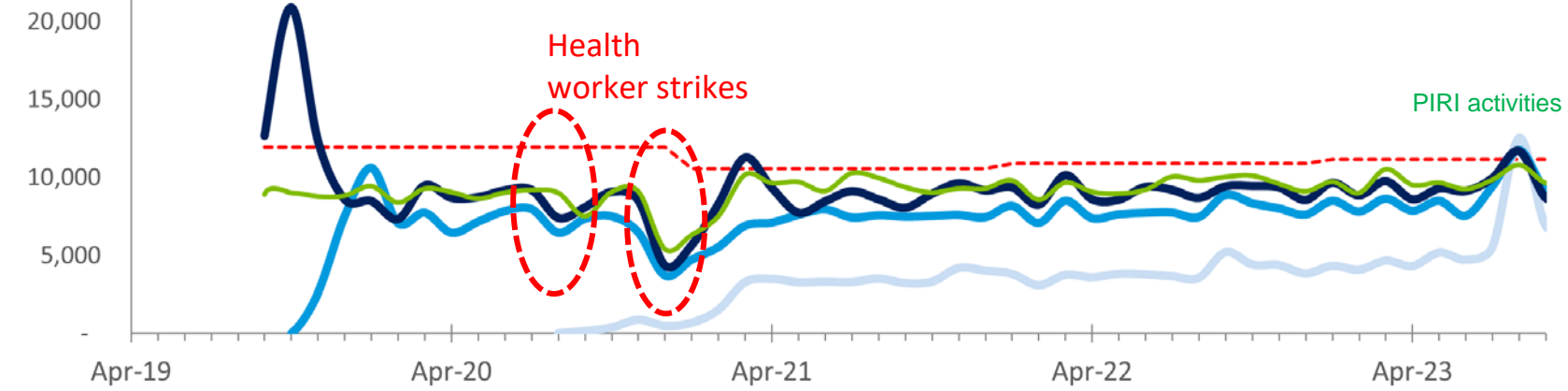
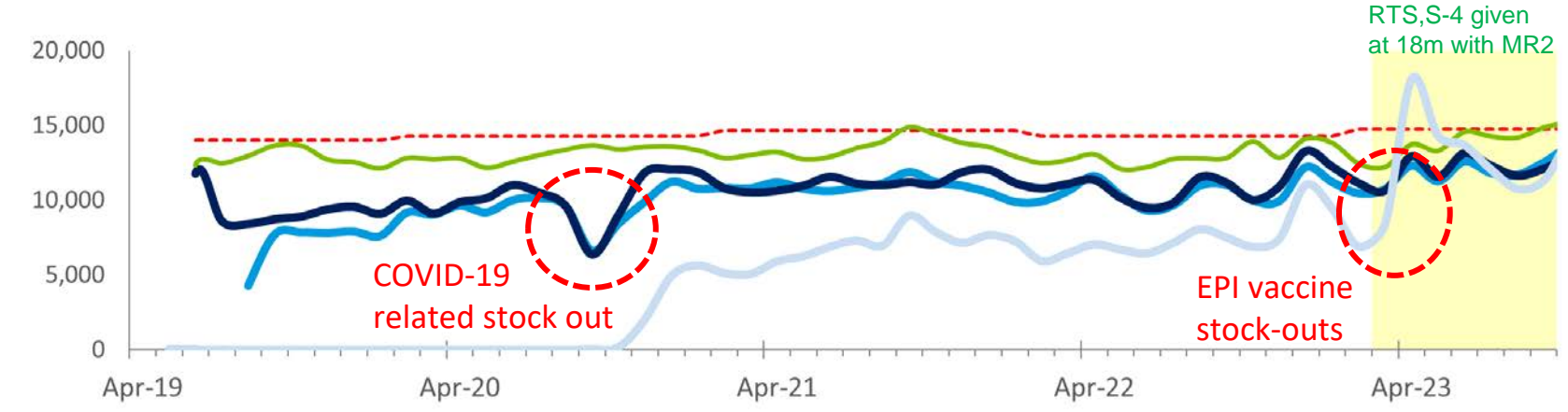
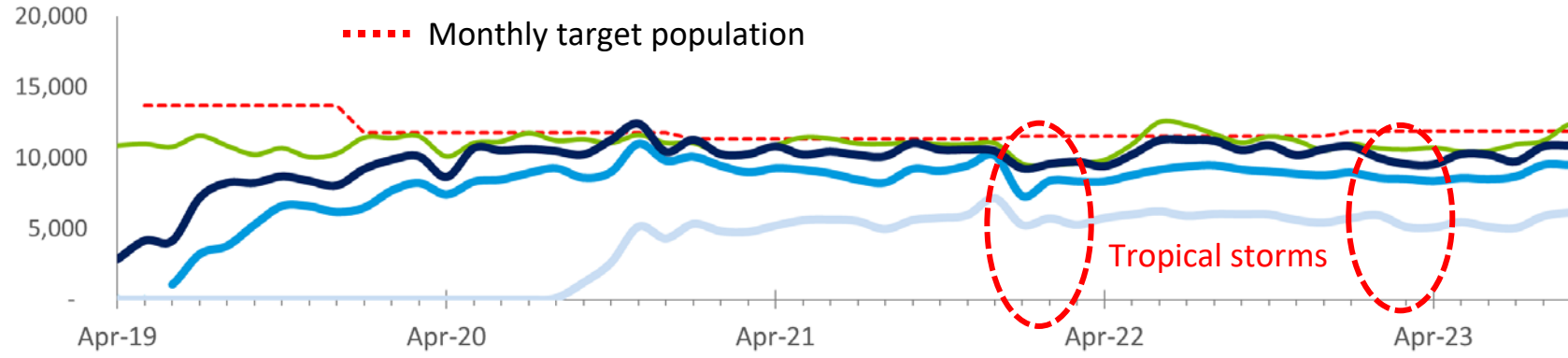
Immunization coverage in initial implementing areas - monthly administrative data reports (through Sept 2023)

| Malawi | 2020 | 2021 | 2022 | Jan-Sept 2023 |
|--|-------------|-------------|-------------|----------------------|
| ■ Penta-3 | 95% | 97% | 95% | 92% |
| ■ RTS,S-1 | 88% | 93% | 90% | 86% |
| ■ RTS,S-3 | 73% | 81% | 76% | 74% |
| ■ RTS,S-4 | | 49% | 50% | 47% |

| Ghana | 2020 | 2021 | 2022 | Jan-Sept 2023 |
|--|-------------|-------------|-------------|----------------------|
| ■ Penta-3 | 92% | 92% | 91% | 94% |
| ■ RTS,S-1 | 71% | 76% | 77% | 82% |
| ■ RTS,S-3 | 66% | 74% | 74% | 81% |
| ■ RTS,S-4 | | 47% | 53% | 83% |

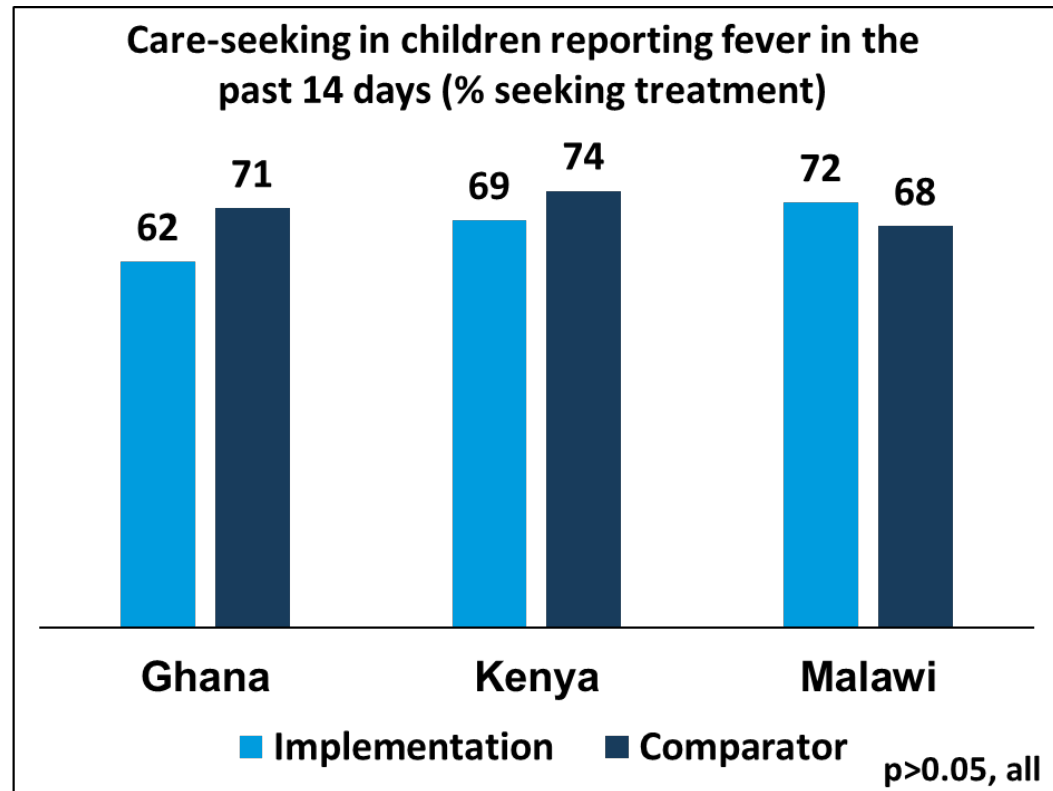
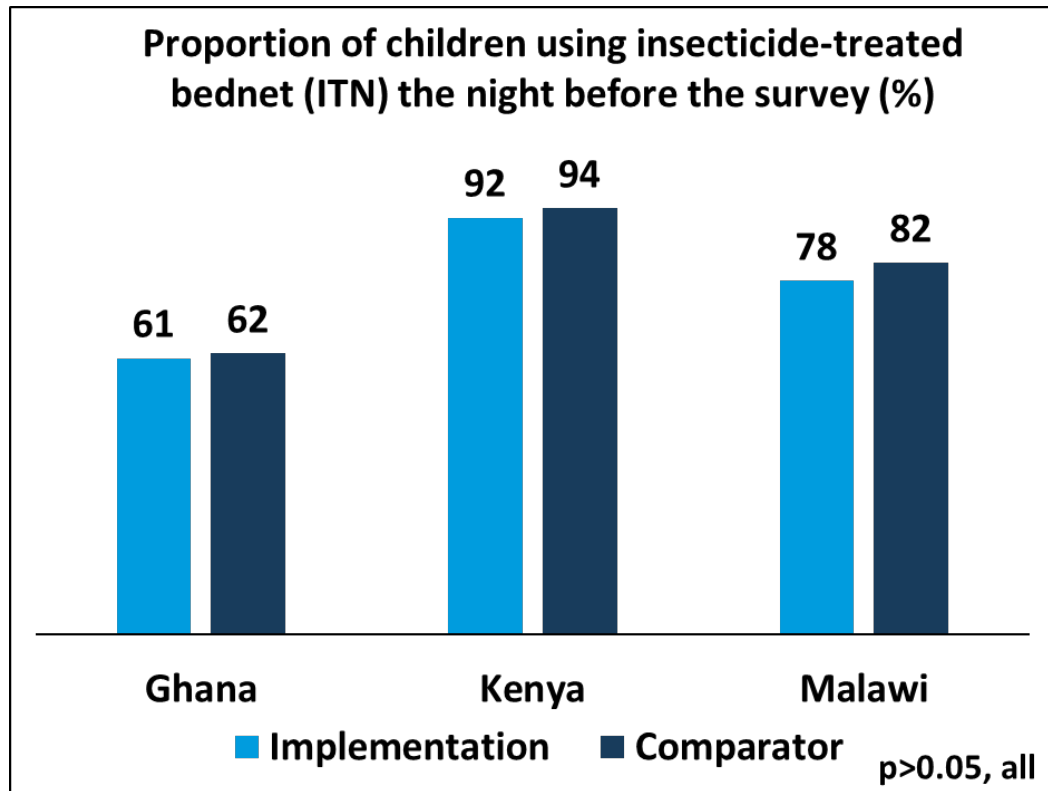
| Kenya | 2020 | 2021 | 2022 | Jan-Sept 2023 |
|--|-------------|-------------|-------------|----------------------|
| ■ Penta-3 | 72% | 87% | 87% | 87% |
| ■ RTS,S-1 | 69% | 82% | 83% | 85% |
| ■ RTS,S-3 | 60% | 67% | 72% | 79% |
| ■ RTS,S-4 | | 29% | 36% | 52% |

Doses administered



No changes in ITN use and care-seeking post RTS,S introduction

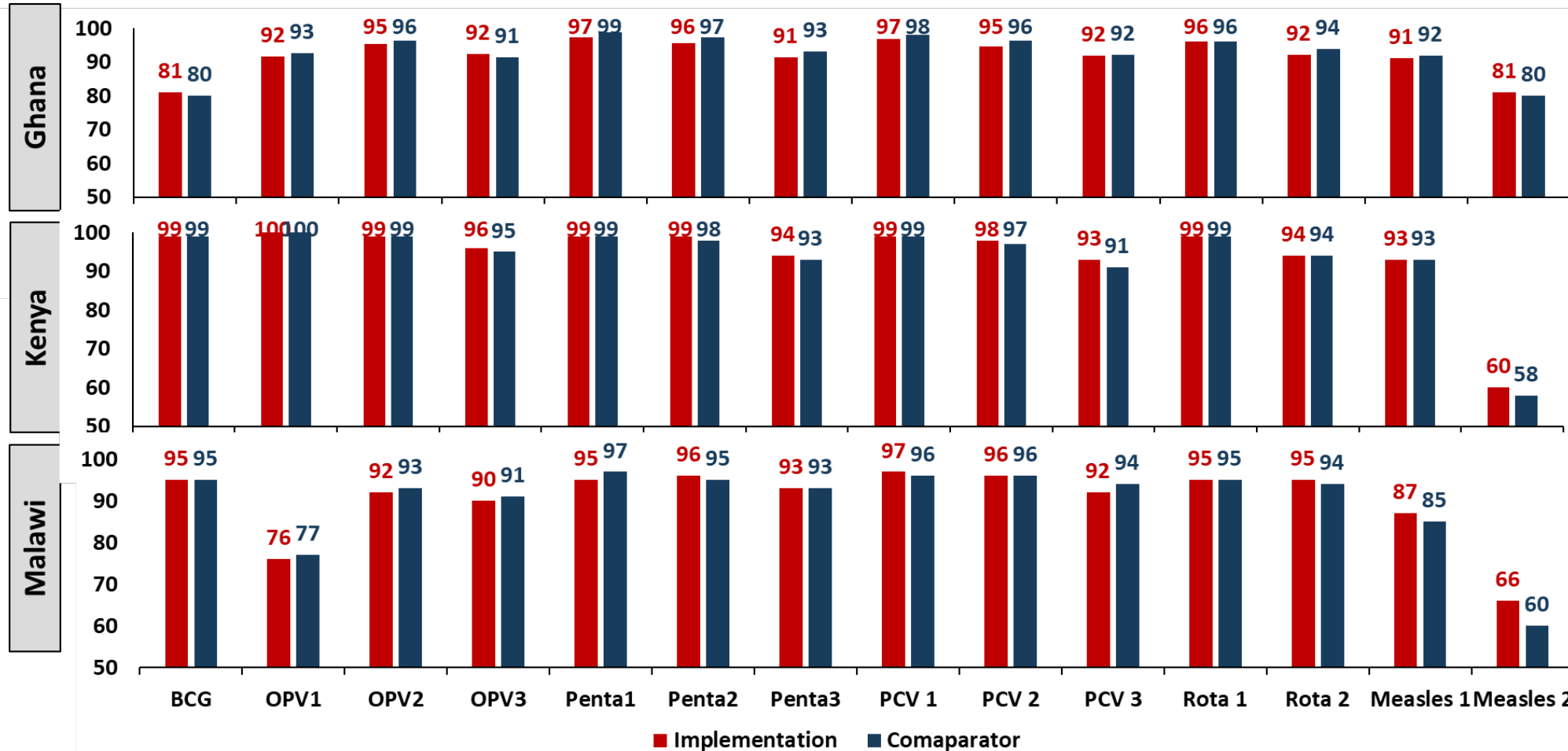
RTS,S/AS01 pilot evaluation endline household surveys (~30 months post introduction)



No changes in ITN use post RTS,S introduction, by study area or over time (except Malawi – changes in ownership and use post ITN campaign, but similar in implementation and control areas). No differences by arm or over time in care-seeking among children reporting fever in past 14 days.

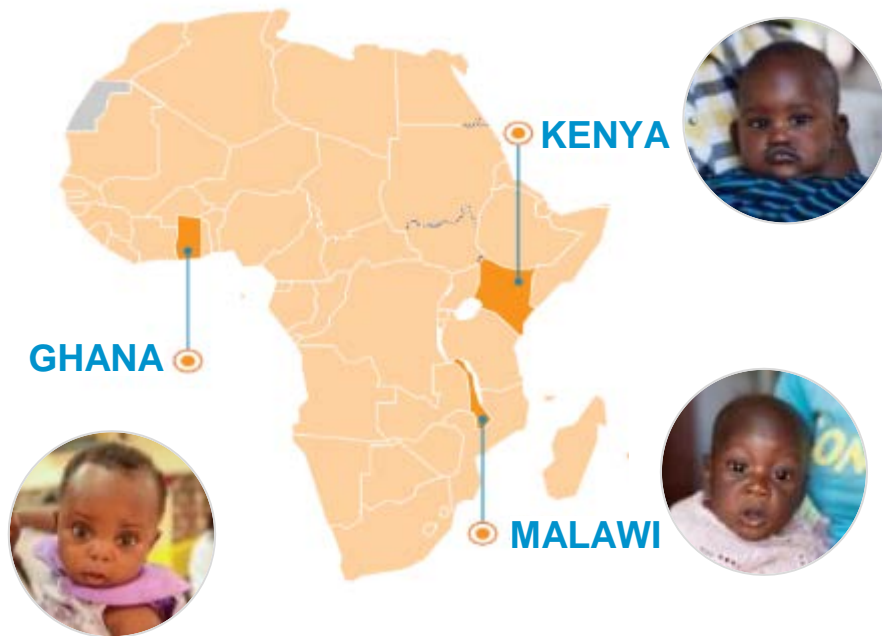
No changes in EPI vaccine coverage by study area or over time

RTS,S/AS01 pilot evaluation endline household surveys (~30 months post introduction)



Findings from the Malaria Vaccine Implementation Programme: 46 months of implementation showing good safety profile, high impact

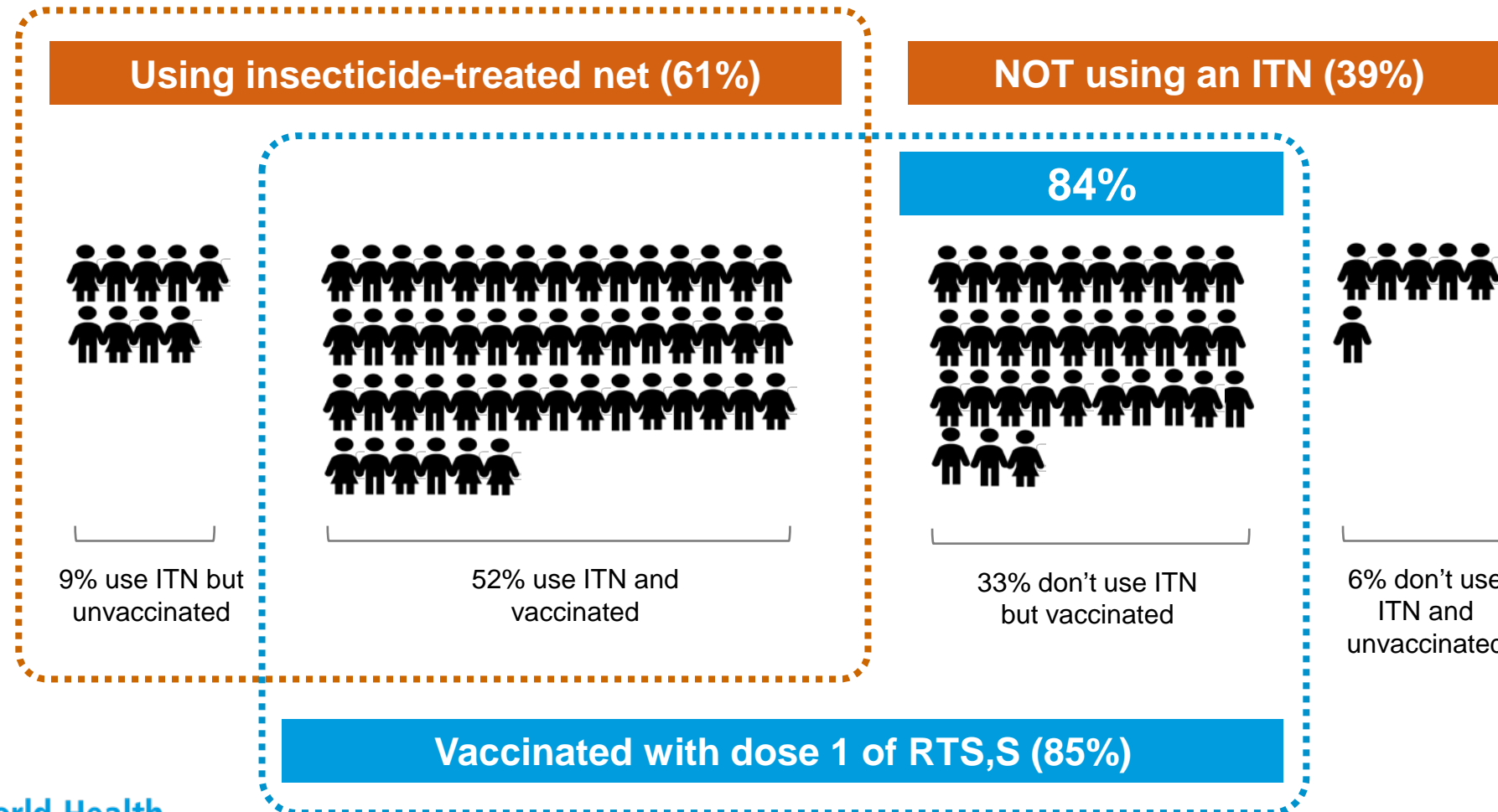
Since 2019, over 2 million children vaccinated with RTS,S/AS01, over 6 million doses administered



- **Vaccine confirmed to be safe** with no evidence of the safety signals in Phase 3 trial, and no new safety signals
- **High impact during 46 months of vaccine introduction:**
 - **13% reduction in all-cause mortality** excluding injury [0.87 (95% CI: 0.78, 0.98)] additional impact on top of that provided by ITNs, IRS and other interventions in place**Impact measured in children age-eligible to receive the vaccine (~64-75% dose 3 coverage, 33-54% dose 4 coverage)**
- **Feasible to introduce with high uptake** and no reduction in ITN use, care seeking behavior or uptake of other vaccines
- **High demand** by community and acceptability by health workers
- **Equity:** Vaccine delivery equitable by gender or SES and extends reach of preventive tools

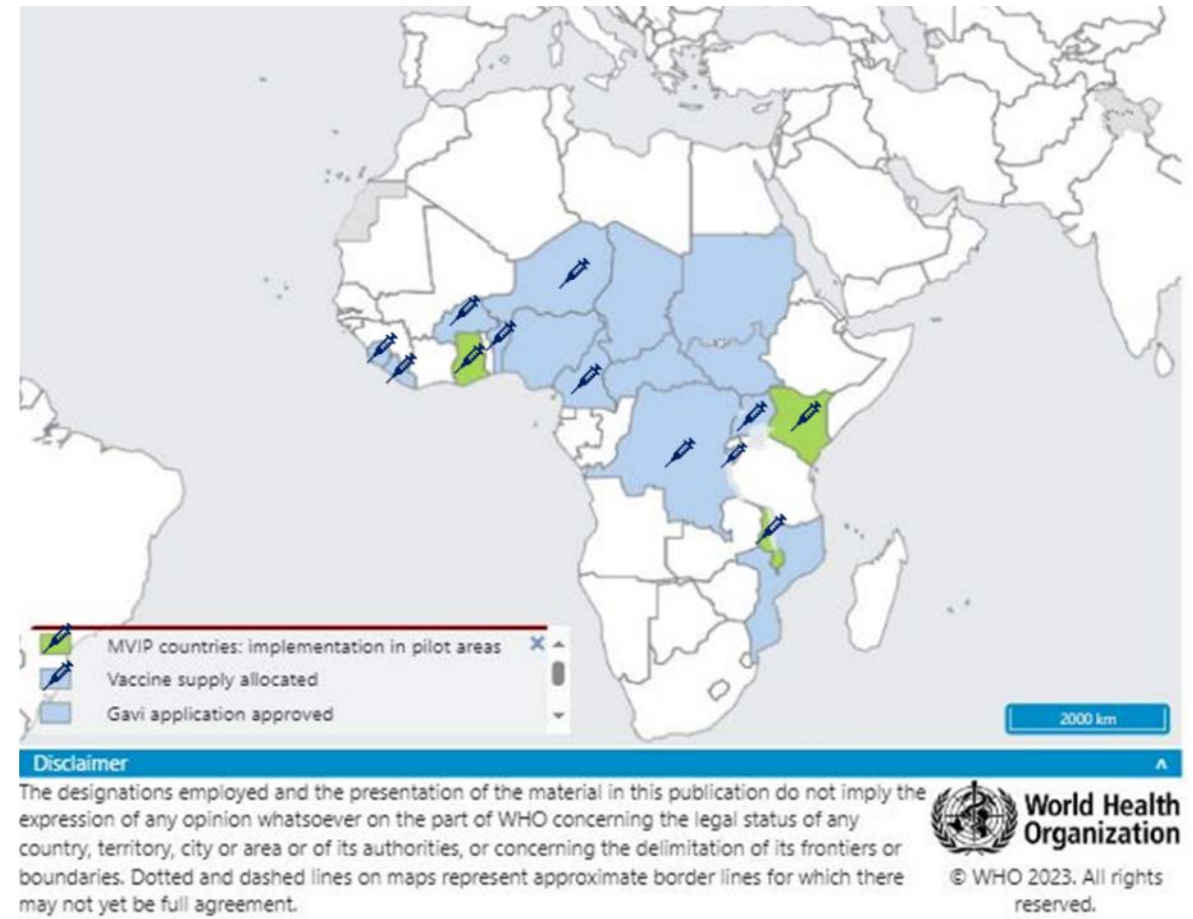
Introduction of a malaria vaccine results in increased access to malaria preventive measures

Ghana household survey after 30 months of vaccine introduction: ITN use and RTS,S children 12-23 months



Countries' Gavi application status for malaria vaccines - as of 28 Nov 2023

- **>30 countries** in Africa interested in introducing a malaria vaccine
- Since opening the funding window in mid-2022, **Gavi approved applications from 18 countries** to introduce vaccine in routine immunization programmes:
 - **Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, DR Congo, Ghana, Kenya, Malawi, Niger, Nigeria, Liberia, Mozambique, Sierra Leone, South Sudan, Sudan, Uganda**
- In July 2023, first supply allocations confirmed for 12 countries (**in bold**) for introduction in Phase 1 (greatest need) areas based on Framework¹



Limited RTS,S supply required prioritization of moderate to high transmission areas based on the principles of the Framework for allocation of limited malaria vaccine supply – Example: Cameroon

Framework

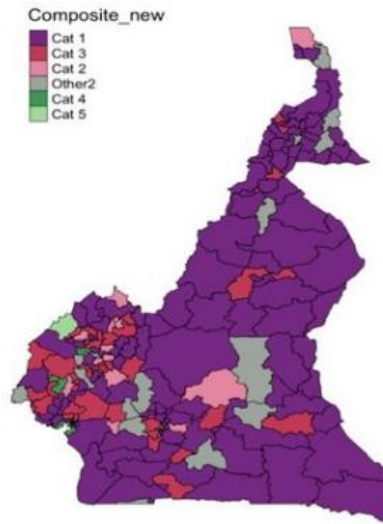
- First allocate to areas of greatest need, where the malaria disease burden in children and risk of death are highest
- Solidarity principle: no country to receive more than 1 million doses per year

| Category of need | Malaria transmission intensity | | All-cause under 5 mortality |
|-----------------------------|--------------------------------|------------------|-----------------------------|
| | Either: Prevalence | OR: U5 Incidence | |
| Category 1 Greatest need | >=40% | >=450 | >=9.5% |
| | >=40% | >=450 | 7.5-9.5% |
| Category 2 | 20-<40% | 350-<450 | >=9.5% |
| | 10-<20% | 250-<350 | >=9.5% |
| | 20-<40% | 350-<450 | 7.5-<9.5% |
| Category 3 | >=40% | >=450 | 6-<7.5% |
| | 10-<20% | 250-<350 | 7.5-<9.5% |
| | 20-<40% | 350-<450 | 6-<7.5% |
| Category 4 | >=40% | >=450 | <6% |
| | 10-<20% | 250-<350 | 6-7.5% |
| Category 5 | 20-<40% | 350-<450 | <6% |
| | 10-<20% | 250-<350 | <6% |

<https://www.who.int/publications/m/item/framework-for-allocation-of-limited-malaria-vaccine-supply>

Country analysis & application to Gavi

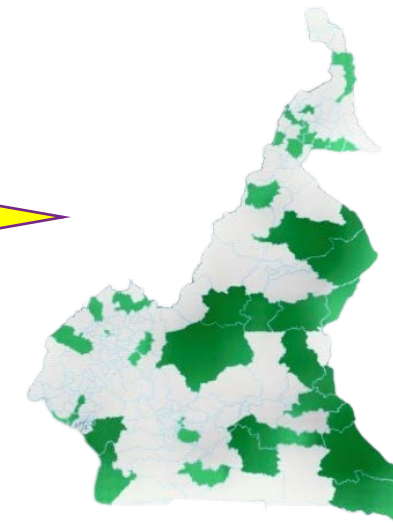
Stratification by category of need



| Cat. | Target population Life births (2023) |
|--------------|---|
| 1 | 697,514 |
| 2 | 69,441 |
| 3 | 156,889 |
| 4 | 7,071 |
| 5 | 1,078 |
| other | 99,599 |
| Total | 1,032,492 |

*Illustrative example of Cameroon analysis in 2022.
Actual implementation may differ.*

Prioritization of areas for Phase 1 roll-out



Target population:
~250,000
children per
year in 42/200
health districts
in 10 regions

- Further prioritization to fit below the cap of 1M doses per year
- A sub-set of category 1 areas prioritized based on country's own criteria

Preparations for malaria vaccine introduction underway

- **Broader rollout of the RTS,S malaria vaccine is underway:** First vaccine shipment arrived in Cameroon, other countries to follow, for introductions starting in coming months
- **Learnings** from MVIP are included in technical guidance to countries
- **Availability of two WHO recommended malaria vaccines is expected to increase supply to meet the high demand from countries** → more information about the implication later in this presentation

First shipment of RTS,S/AS01 arrived

↻ MinsanteCameroun reposted



Dr MANAOUA MALACHIE @Dr... · 8h ...

J'ai réceptionné, ce mardi 21 novembre 2023, 331.200 doses de vaccin contre le paludisme. Le Cameroun devient ainsi le pionnier en la matière. Un moment historique facilité par nos partenaires pour booster la lutte contre cette maladie responsable de 70% des décès chez les enfants



13 13 36 3.1K

Dr Manaouda Malachie, MoH Cameroon, receiving the country's first shipment of RTS,S dose; 21 November 2023



R21/Matrix-M: Safety, efficacy and impact data & WHO recommendation

Lindsey Wu and Rafiq Okine, WHO

WHO press briefing on SAGE meeting outcomes, 2 October 2023



WHO recommends R21/Matrix-M vaccine for malaria prevention in updated advice on immunization

2 October 2023 | News release | Geneva | Reading time: 5 min (1351 words)

The World Health Organization (WHO) has recommended a new vaccine, R21/Matrix-M, for the prevention of malaria in children. The recommendation follows advice from the WHO: Strategic Advisory Group of Experts on Immunization (SAGE) and the Malaria Policy Advisory Group (MPAG) and was endorsed by the WHO Director-General following its regular biannual meeting held on 25-29 September.

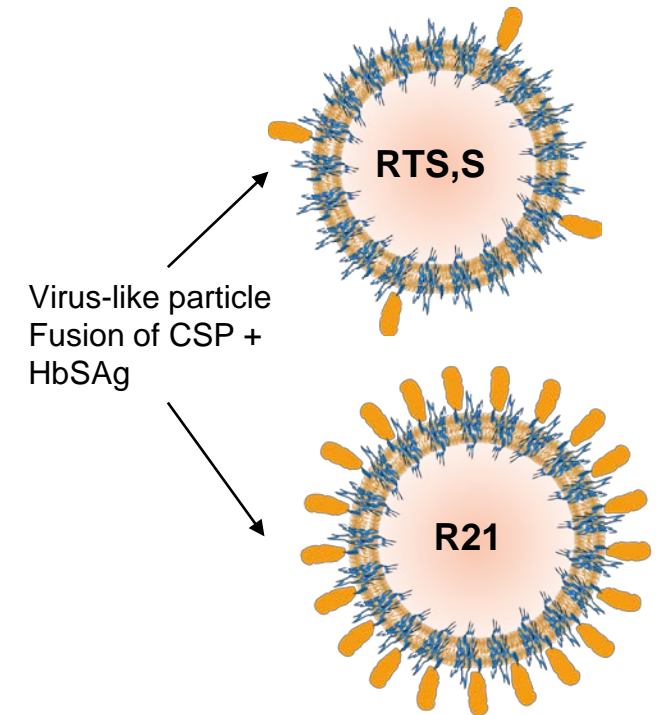
WHO also issued recommendations on the advice of SAGE for new vaccines for dengue and meningitis, along with immunization schedule and product recommendations for COVID-19. WHO also issued key immunization programmatic recommendations on polio, IA2030 and recovering the immunization programme.

The R21 vaccine is the second malaria vaccine recommended by WHO, following the RTS,S/AS01 vaccine, which received a WHO recommendation in 2021. Both vaccines are shown to be safe and effective in preventing malaria in children and, when implemented broadly, are expected to have high public health impact. Malaria, a mosquito-borne disease, places a particularly high burden on children in the African Region, where nearly half a million children die from the disease each year.

WHO Press release: <https://www.who.int/news/item/02-10-2023-who-recommends-r21-matrix-m-vaccine-for-malaria-prevention-in-updated-advice-on-immunization>

R21/Matrix-M malaria vaccine background

- **Second malaria vaccine to be reviewed by WHO for recommendation**
- **Similar to RTS,S/AS01 with regards to:**
 - **Mechanism of action and indication**
 - Pre-erythrocytic vaccine - reduction of *P. falciparum* malaria
 - Target population - infants and young children
 - **Vaccine construct and adjuvant**
 - Virus-like particle platform
 - Formulated with Matrix-M adjuvant, saponin extract (similar to AS01)
 - **Schedule**
 - 3 dose primary series (given 1 month apart)
 - 4th dose given 12 months after dose 3
 - Seasonal or age-based delivery



R21/Matrix-M evidence review process

| Groups involved | Key dates |
|---|--|
| SAGE/MPAG Working Group on Malaria Vaccines | Initial evidence review (7-8 March 2023) Full evidence review (25-27 July 2023) Additional teleconference (21 Sept 2023) |
| R21/Matrix-M Safety Working Group | Safety evidence review (20 June 2023) |
| African Advisory Committee on Vaccine Safety (AACVS) | Briefed by WHO Secretariat (May 2023) |
| Global Advisory Committee on Vaccine Safety (GACVS) <ul style="list-style-type: none">• Received input from R21/Matrix-M Safety Working Group• Included representation from AACVS and R21/Matrix-M DSMB | Safety evidence review (30 June 2023) |
| SAGE and MPAG in joint session (following SAGE processes) | Technical briefing (5 Sept 2023) Joint session (27 Sept 2023) |
| WHO Prequalification (PQ) | Dossier accepted Q1 2023; review ongoing as per ordinary PQ processes |

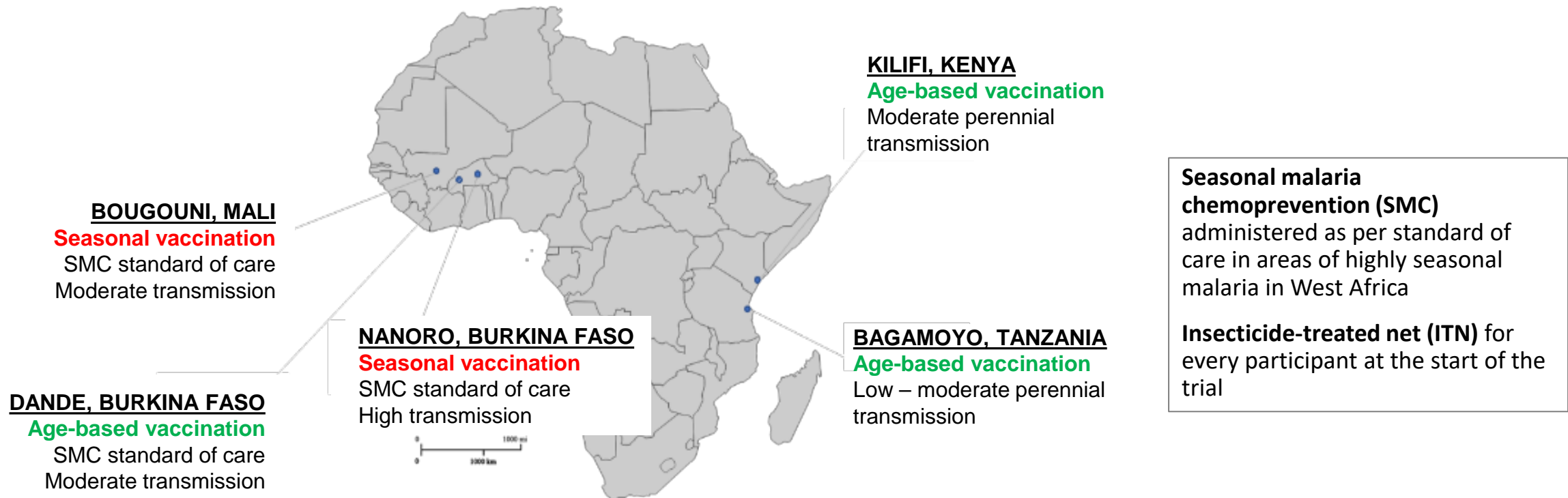
WHO evidence review based on Phase 3 clinical trial data

**Seasonal administration (n=2,400),
ages 5-36 months at first vaccination**

- 2 sites: Nanoro, Burkina Faso and Bougouni, Mali

**Age-based (“standard”) administration
(n=2,400), ages 5-36 months at first vaccination**

- 3 sites: Dande, Burkina Faso; Kilifi, Kenya and Bagamoyo, Tanzania



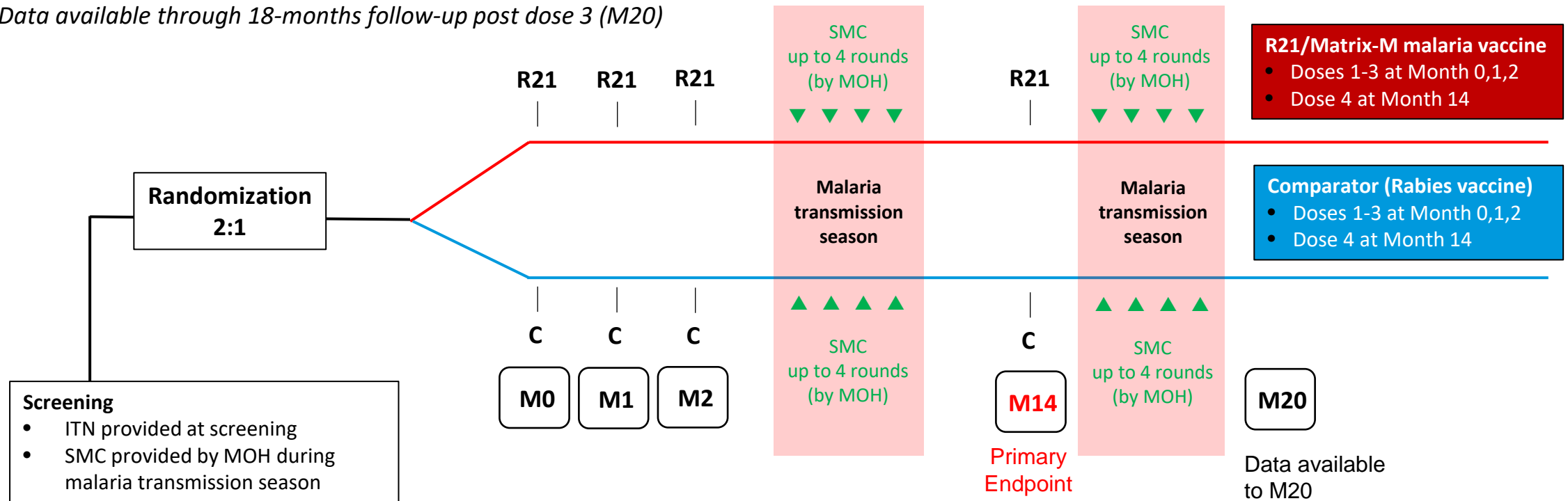
R21/Matrix-M Phase 3 Trial Design: Seasonal administration in areas of highly seasonal transmission

n=2400, ages 5-36 months at first vaccination

2 sites: Nanoro, Burkina Faso and Bougouni, Mali

Primary endpoint (shown in red): 12 months post dose-3 (M14)

Data available through 18-months follow-up post dose 3 (M20)



C=Comparator (Rabies vaccine); M=study month

Recruited according to age group (5-12 months, 13-24 months, 25-36 months), gender and site

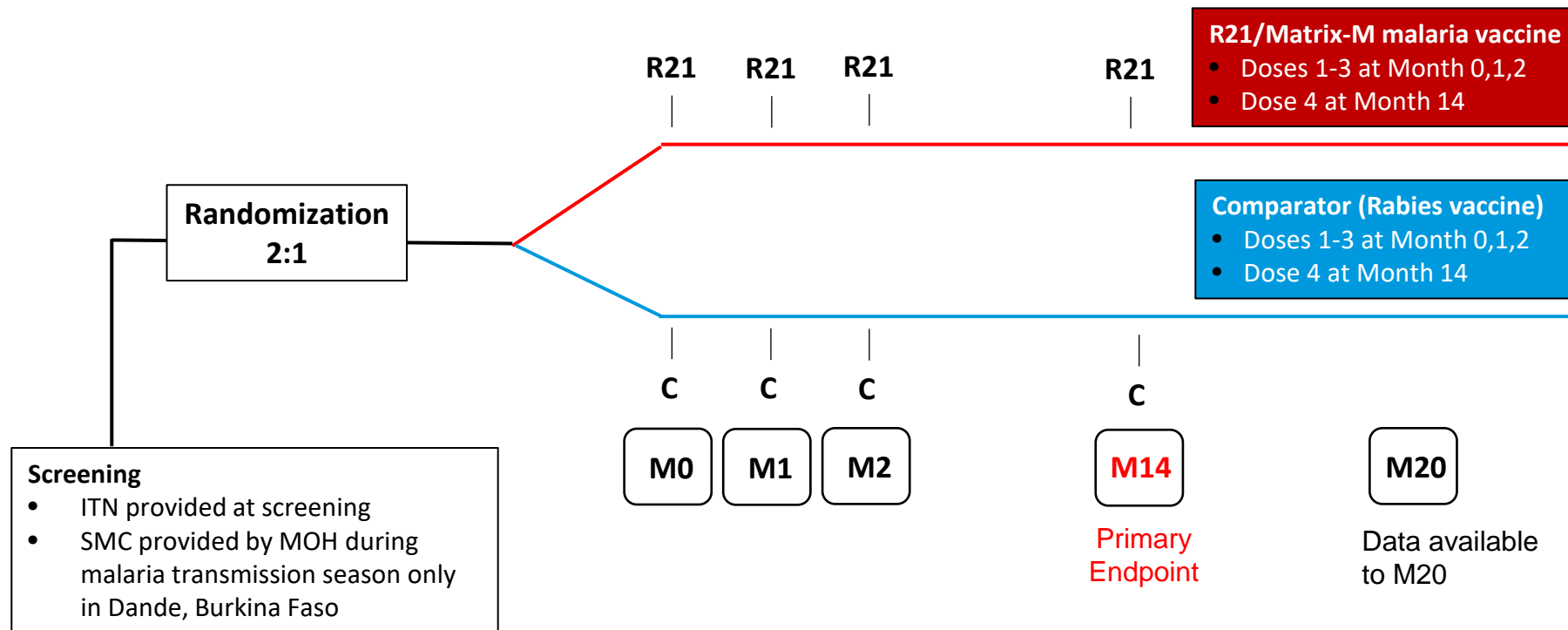
R21/Matrix-M Phase 3 Trial Design: *Age-based (“standard”) administration*

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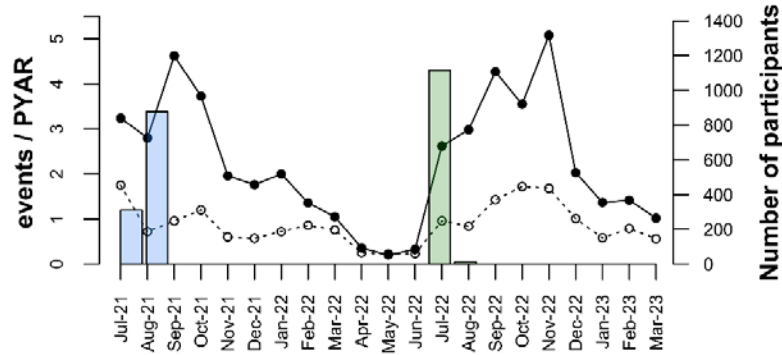


C=Comparator (Rabies vaccine); M=study month

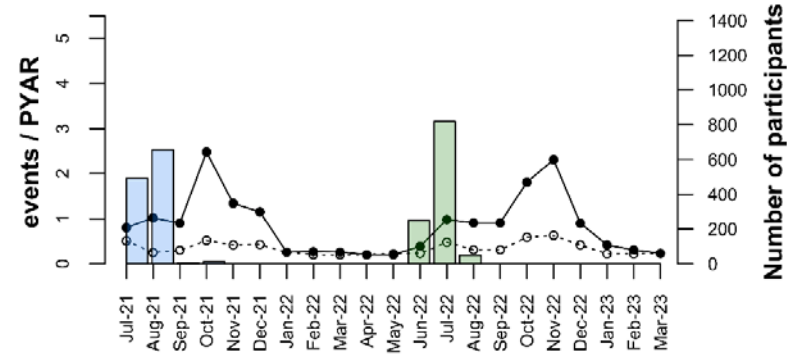
Recruited according to age group (5-12 months, 13-24 months, 25-36 months), gender and site

Malaria transmission intensity by study site

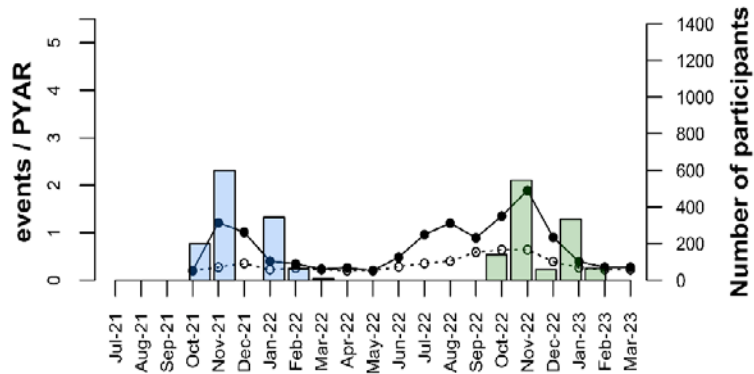
A. Nanoro, Burkina Faso (seasonal)



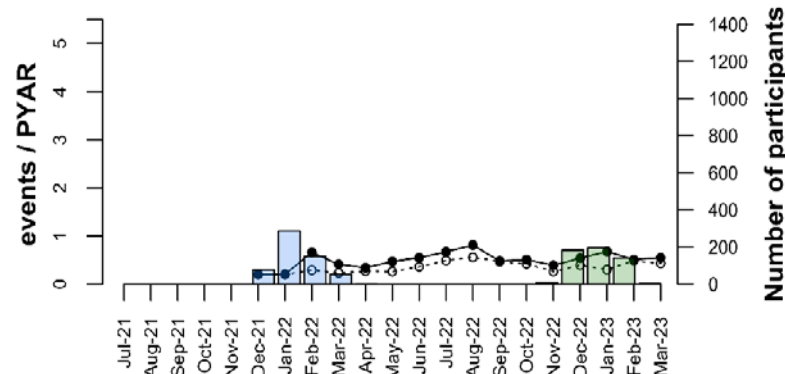
B. Bougouni, Mali (seasonal)



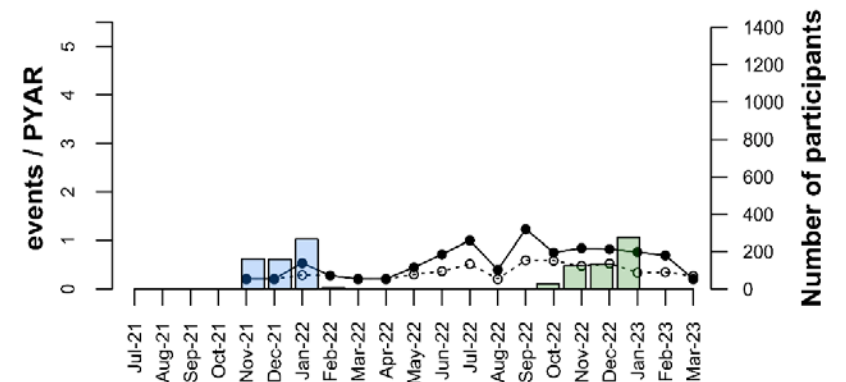
C. Dande, Burkina Faso (standard)



D. Bagamoyo, Tanzania (standard)



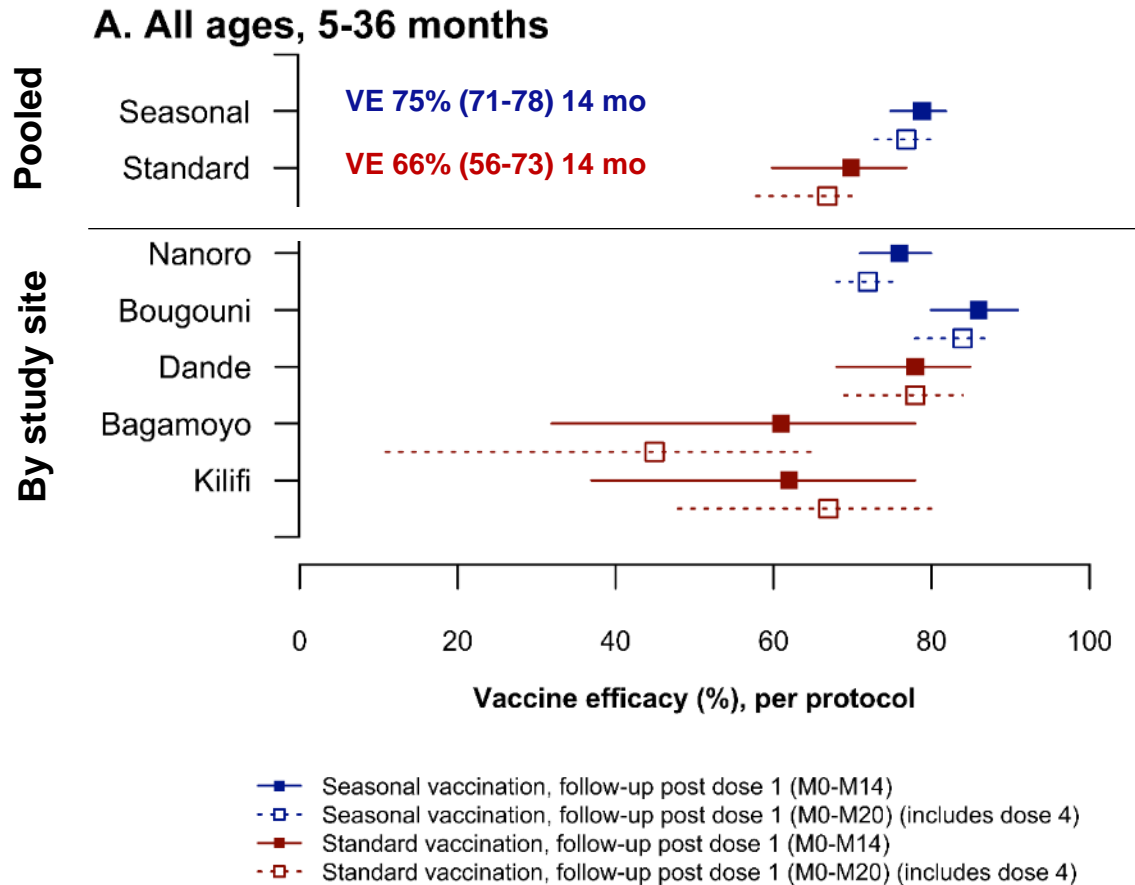
E. Kilifi, Kenya (standard)



- Rate of clinical malaria, control arm
- Rate of clinical malaria, R21/Matrix-M arm
- Dose 3 + 14 days, number of participants beginning follow-up
- Dose 4, number of participants beginning follow-up

R21 vaccine efficacy against all episodes of clinical malaria, *per protocol*

Seasonal sites, 14- and 20-month follow-up post dose 1 (blue); Standard sites, 14-month follow-up post dose 1 (red)

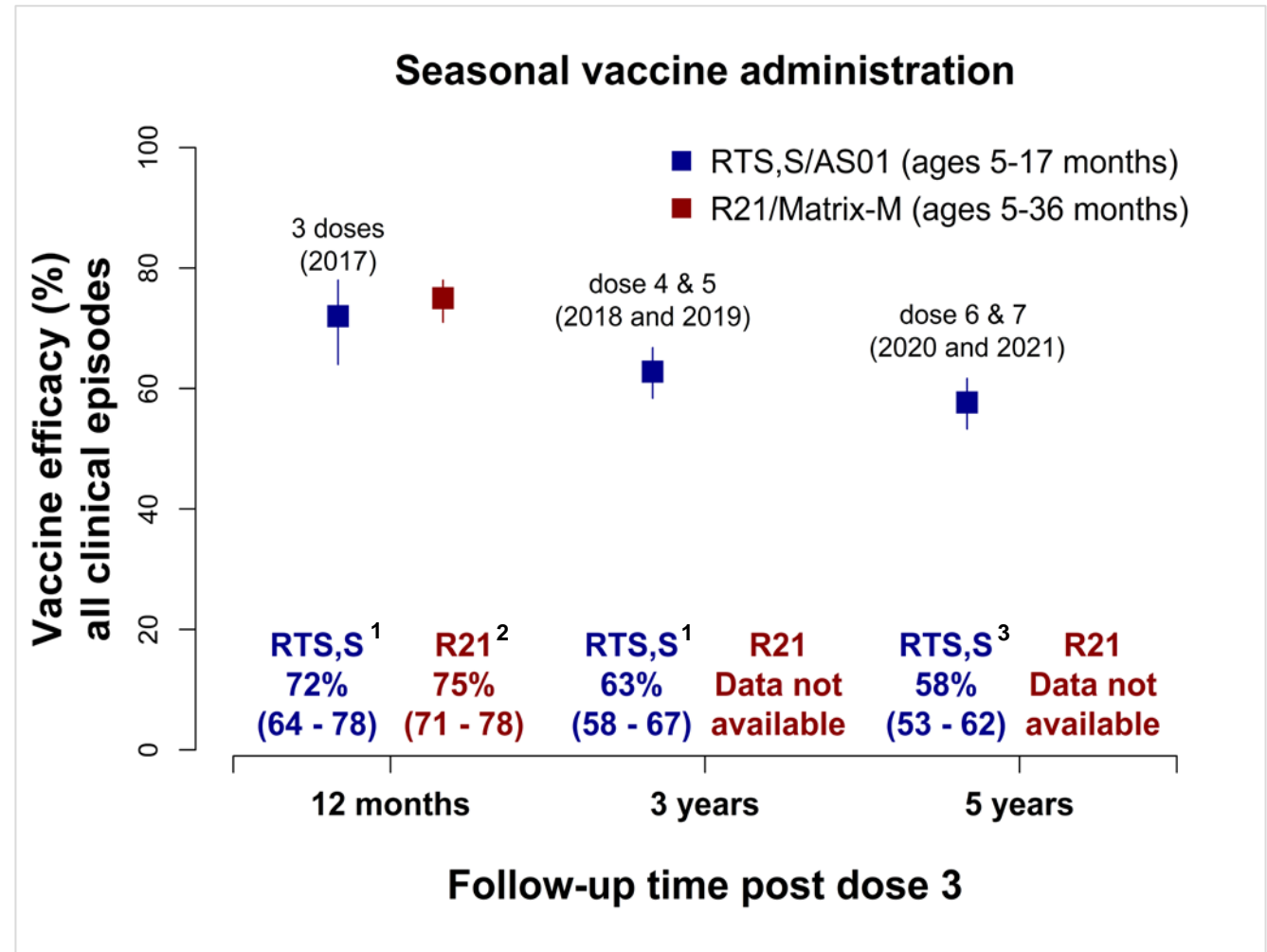


- Efficacy similar 12 months after 3 doses and 6 months after dose 4
- Efficacy lower in East African sites (Bagamoyo, Kilifi)
 - Perennial transmission, age-based vaccination
- No significant differences in VE between boy and girls
- VE for the younger 5-17 month age group slightly lower than 18-36 month age group, but with overlapping 95% CIs
- VE similar according to the number of rounds of SMC received, but limitations to data*

*study not designed to measure SMC effect, SMC provided through MOH with varying coverage, ascertainment of SMC through home health cards, no written documentation of SMC given on health card interpreted as zero SMC received

Efficacy of seasonal vaccination schedule with SMC

- **R21 has high efficacy when given prior to the high transmission season**
 - **75% (95% CI 71 - 78)**
 - 12 months after a 3-dose series
- **RTS,S has similar efficacy when given seasonally¹**
 - **72% (95% CI 64 - 78)**
 - 12 months 3-dose series
- **3- and 5-year follow-up data on R21 not yet available**



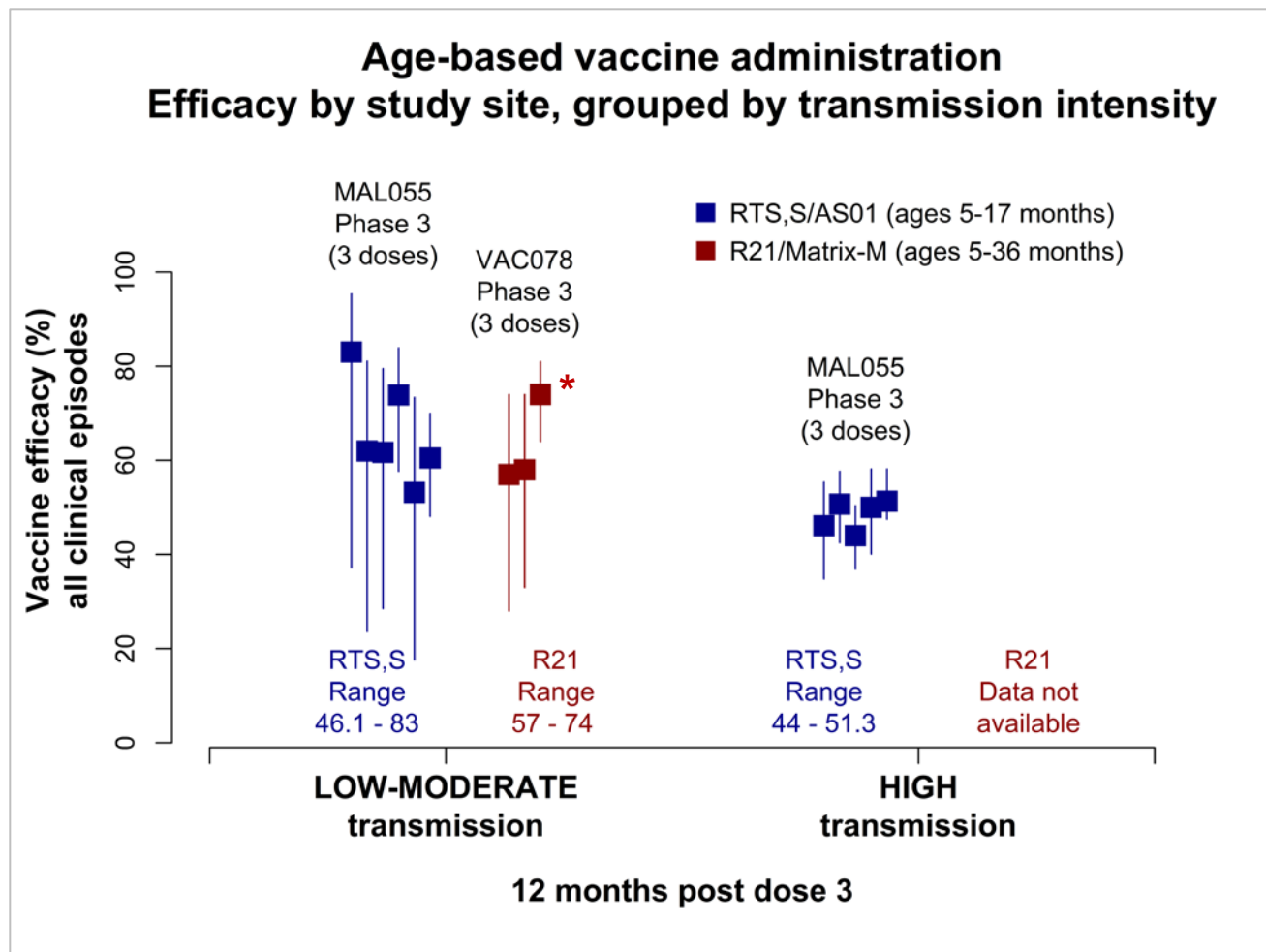
Efficacy of age-based vaccination schedule

- **R21 showed good efficacy when given in an age-based schedule**
 - **66% (95%CI 56-73)** 12 months after 3 doses in moderate to low perennial transmission settings.
 - A fourth dose a year after the third maintained efficacy
- R21 has not been tested in areas of *high perennial transmission*, but is expected have similar level of impact as RTS,S
- **The two vaccines have not been tested in a head-to-head trial, and there is no evidence that one vaccine performs better than the other**

Efficacy of age-based vaccination

- **Evaluation of age-based vaccination in RTS,S and R21 Phase 3 trials were in different ranges of transmission intensity**
 - RTS,S MAL055: High, Moderate, Low
 - R21 VAC078: Only Moderate & Low
- **As observed in the RTS,S trial, efficacy can vary substantially by transmission intensity**
- Efficacy of RTS,S available up to 48mo
- Data on longer-term efficacy of R21 (>18 months) not yet available

Efficacy at 12 months post dose 3 *by transmission intensity*



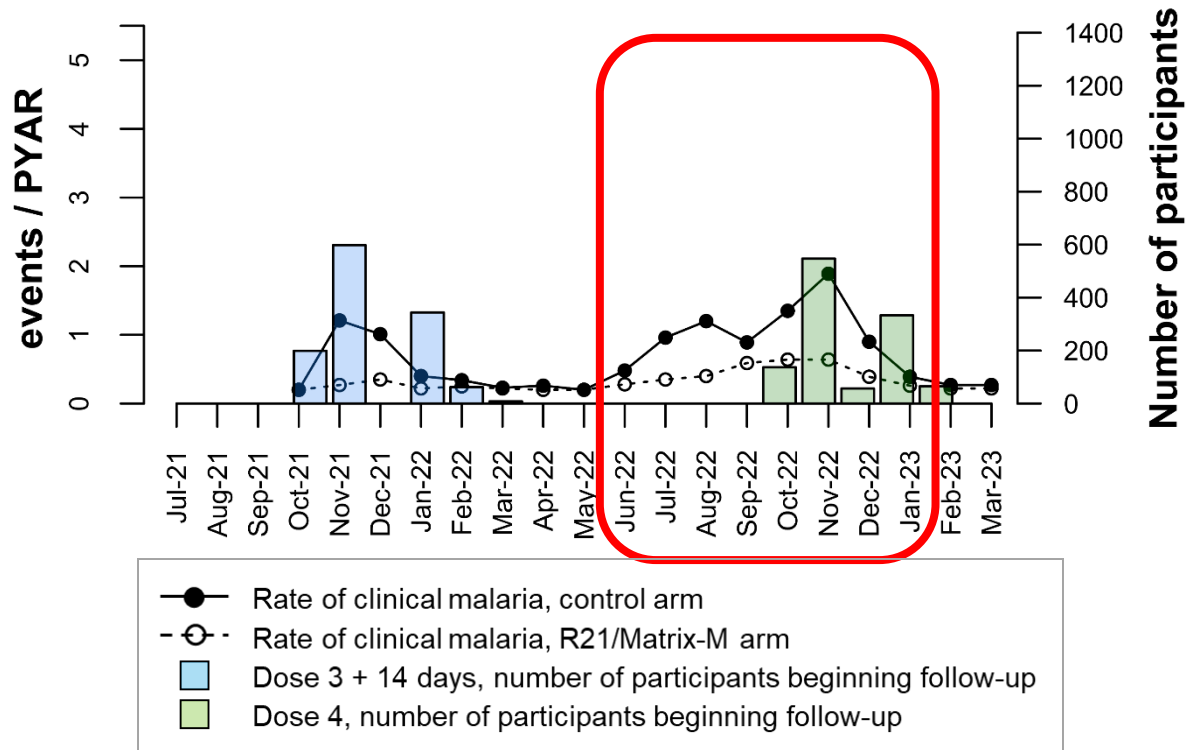
- **Similar range of efficacy for R21 and RTS,S study sites in low-moderate transmission (12 months post dose 3)**
- RTS,S efficacy range in low-moderate transmission greater than efficacy in high transmission study sites
- No data for efficacy of R21 age-based vaccination in high transmission settings
- Dandé (seasonal setting where SMC was standard of care) was the R21 study site with highest efficacy using age-based vaccination

Site-specific point estimates from MAL055 and VAC078 trials shown in order of increasing transmission intensity from left to right

* Dandé study site received SMC from MOH

Duration of protection of age-based vaccination in moderate transmission setting

C. Dande, Burkina Faso (standard)



- While no data on age-based administration in high perennial transmission
 - Data from moderate seasonal transmission – Dandé, Burkina Faso - gives some evidence on duration of protection
- Despite not timing primary doses prior to 1st peak season, high efficacy during 2nd seasonal peak in malaria transmission 6 months after dose 3, prior to dose 4 admin
- Vaccine efficacy 12 months post dose 3 was 74% (65 - 81)

Evidence on R21/Matrix-M (R21) malaria vaccine

- **High impact:** Initial mathematical modelling estimates indicate the public health impact of the R21 vaccine is expected to be high in a wide range of malaria transmission settings
- **Cost effectiveness:** At a price range assumption of US\$ 2 – US\$ 4 per dose, the cost-effectiveness of the R21 vaccine would be comparable with other recommended malaria interventions and other childhood vaccines
- **Safety:** No major safety concerns were noted that would warrant a delay in recommendation of R21 malaria vaccine for public health use
- **Similarity of R21 and RTS,S vaccines:** The R21 vaccine is similar to RTS,S in construct, target population, and delivery strategy. There is no evidence that one vaccine performs better than the other
- **Price:** The initial price of R21/Matrix-M vaccine has been announced at US\$ 3.90 per dose, considerably lower than the initial price for RTS,S/AS01 (EUR 9.30 per dose)

WHO R21/Matrix-M malaria vaccine evidence review resources available to NITAGs



Full evidence report for R21/Matrix-M malaria vaccine

<https://www.technet-21.org/en/topics/programme-management/malaria-vaccine> (section: decision making)

Report annex include:

- **GRADE evidence table**
- **Evidence to Recommendation Table**

R21 GRADE Tables (SAGE Yellow Book page 16, 7.2)

| Outcome | Comparison | Study design | N ^o of participants | | Relative effect (95% CI) | Absolute effects (95% CI) | | Certainty | Comments |
|---|---|---|--------------------------------|------------------------------|------------------------------------|---|--|-----------|---|
| | | | Vaccination | Control | | Control | Risk difference with malaria vaccination | | |
| CLINICAL MALARIA (Impact, critical outcome) | R21/Matrix-M versus control ²⁰ | Ph 2b randomised trial; 2019-2021; (12 months follow-up post dose 3) | 39/146 (27%) | 106/147 (72%) | VE: 77% (67% to 84%) ²¹ | 106/147 (720 per 1000) | 555 fewer per 1000 (606 fewer to 483 fewer) | ⊕⊕⊕⊕ HIGH | R21/Matrix-M vaccination reduces clinical malaria cases |
| | | | | | | Study population | | | |
| | R21/Matrix-M versus control ²² | Ph 3 randomised trial; 2019-ongoing (month 0-month 20; 18 months follow-up post-dose 3) | 932/1613 (57.8%); 2665 PYAR | 1688/811 (208.1%); 1335 PYAR | VE: 74% (70% to 76%) ²³ | 1688/1335 PYAR | 936 fewer per 1000 PYAR (961 fewer to 885 fewer) | ⊕⊕⊕⊕ HIGH | R21/Matrix-M vaccination reduces clinical malaria cases |
| | | | | | | Low transmission | | | |
| | | | | | | No Phase 3 trial sites with seasonal administration in low transmission areas | | | |
| | | | | | | Moderate to high transmission ²⁴ | | | |
| | | | | | | 534 per 1000 PYAR | 450 fewer cases per 1000 PYAR | | |
| | | | | | | High transmission ²⁵ | | | |
| 1515 per 1000 PYAR | 1229 fewer cases per 1000 PYAR | | | | | | | | |

R21 Evidence to Recommendation Table (SAGE Yellow Book page 16, 7.3)

Strategic Advisory Group of Experts (SAGE) on Immunization Evidence to recommendations framework¹

Include summary of:

- **Benefits and Harms**
- **Values and preferences**
- **Resource requirements**
- **Cost-effectiveness**
- **Impact on health inequities**
- **Acceptability**
- **Feasibility**

| |
|---|
| <p>Question: Should a malaria vaccine be provided to reduce malaria disease burden in children ≥ 5 months of age living in regions with endemic malaria transmission?</p> <p>Population: Children ≥ 5 months of age</p> <p>Intervention: Malaria vaccination according to recommended schedule</p> <p>Comparison: Malaria prevention interventions currently in place without malaria vaccination</p> <p>Setting: regions with endemic high, moderate, or low malaria transmission (as defined by WHO²)</p> |
| <p>Background: Malaria is one of the leading causes of childhood illness and deaths in Africa. All malaria control interventions provide only partial protection against malaria and the highest impact is achieved when interventions are strategically used together. The RTS,S/AS01 malaria vaccine was recommended by WHO in 2021 to prevent malaria in children living in regions with moderate-to-high <i>P. falciparum</i> malaria transmission. As of August 2023, over 1.8 million children have received at least 1 dose of the RTS,S/AS01 vaccine through phased introductions that began in 2019 in Ghana, Kenya, and Malawi. Results from pilot evaluations in those three countries (recommended by WHO in 2015) affirm the malaria vaccine is feasible to deliver, is safe and reduces childhood malaria, hospitalizations, and deaths.</p> <p>Demand for a malaria vaccine is very high, estimated to reach 40–60 million doses by 2026 and growing to 80–100 million doses per year or more each year by 2030. However, the initial supply of RTS,S/AS01 is insufficient to meet demand. A second malaria vaccine, in addition to RTS,S/AS01, could help close the gap between supply and demand—enabling broader access and saving tens of thousands of lives each year.</p> <p>This Evidence to recommendations framework summarizes evidence available on the R21/Matrix-M malaria vaccine for potential inclusion within the current WHO malaria vaccine recommendation (see 2021 Evidence to recommendations framework on RTS,S/AS01 for more details on the global malaria vaccine evidence available).³</p> <p>A Phase 3 clinical trial began in late April 2021 to assess the safety and protective efficacy of the R21/Matrix-M malaria vaccine against clinical malaria caused by <i>P. falciparum</i> in children 5–36 months of age at first vaccination using a seasonal administration approach in sites with highly</p> |

WHO recommendation: malaria vaccines

WHO recommends the programmatic use of malaria vaccines for the prevention of *P. falciparum* malaria in children living in malaria endemic areas, prioritizing areas of moderate and high transmission

- The malaria vaccine should be provided in a schedule of 4 doses in children from around 5 months of age¹ for the reduction of malaria disease and burden
- A 5th dose, given one year after dose 4, may be considered in areas where there is a significant malaria risk remaining in children a year after receiving dose 4
- Countries may consider providing the vaccine using an age-based, seasonal, or a hybrid of these approaches in areas with highly seasonal malaria or areas with perennial malaria transmission with seasonal peaks
- Countries should prioritize vaccination in areas of moderate and high transmission, but may also consider providing the vaccine in low transmission settings
- Vaccine introduction should be considered in the context of comprehensive national malaria control plans

¹ Vaccination programmes may choose to give the first dose at a later or earlier age based on operational considerations. Studies with RTS,S/AS01 indicated lower efficacy if first dose was given around 6 weeks of age. However, it seems unlikely that efficacy would be substantially reduced if some children received the first dose at 4 rather than 5 months, and providing vaccination at an age younger than 5 months may increase coverage or impact

This recommendation now includes two malaria vaccines:

- **RTS,S/AS01**
WHO pre-qualified in 2022
- **R21/Matrix-M**
WHO pre-qualification review ongoing

WHO recommendation: malaria vaccine dose schedule and delivery

- In areas of perennial malaria transmission, the malaria vaccine should be provided as a 3-dose primary series, starting from around 5 months of age, with a minimal interval of 4 weeks between doses
- The fourth dose should be given to prolong protection. There can be flexibility to optimize delivery for dose 4:
 - Alignment with other vaccines in the second year of life
 - Administration prior to seasonal peaks to optimize efficacy
 - The optimal interval between dose 3 and 4 has not been established
- If malaria remains a significant public health problem in children a year after the fourth dose, then a fifth dose might be considered, depending on a local assessment of feasibility and cost-effectiveness

Product Choice: There is no evidence that one vaccine performs better than the other. **Country decisions on which vaccine to introduce should be made on programmatic characteristics, such as affordability and supply to scale-up**

This recommendation now includes two malaria vaccines:

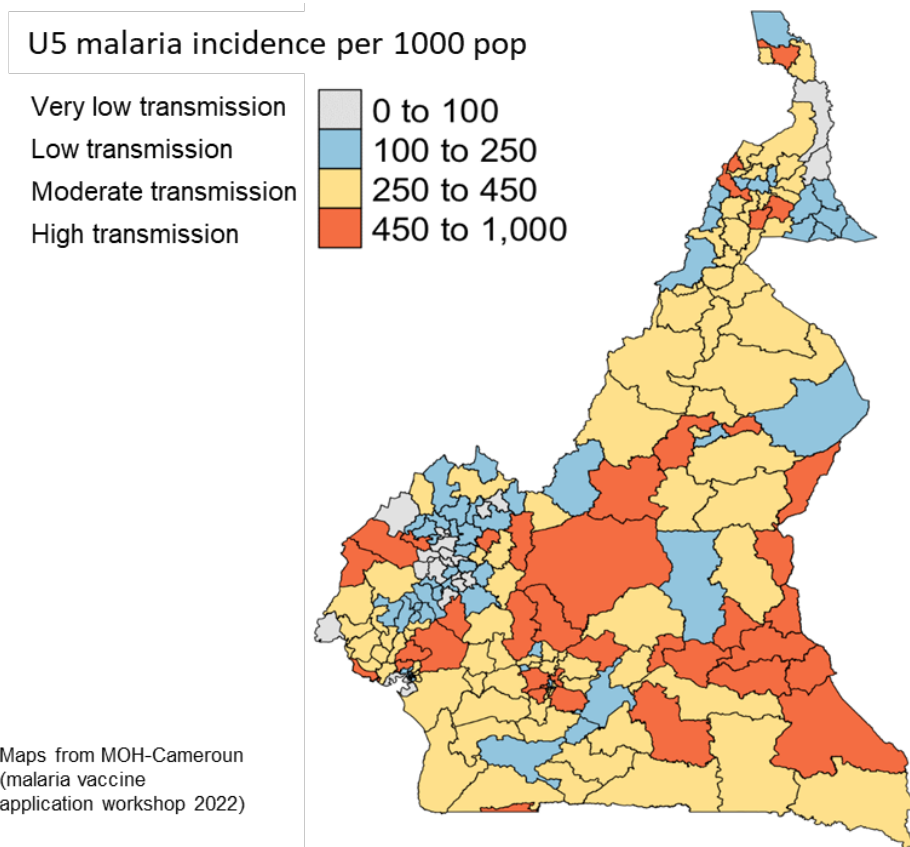
- **RTS,S/AS01**
WHO pre-qualified in 2022
- **R21/Matrix-M**
WHO pre-qualification review ongoing

Malaria vaccines in low transmission setting

Permissive recommendation:

Potential to improve feasibility of delivery if lower transmission areas are next to higher transmission areas

Illustrated by the stratification of malaria burden for vaccine introduction in Cameroun below



- Both R21/Matrix-M and RTS,S/AS01 are efficacious in areas of low malaria transmission.
- Clinical trial data and mathematical modelling estimate considerable impact, including in areas of low malaria transmission.
- **Decisions on vaccine introduction should be made at a country level**
 - As part of overall, comprehensive malaria control plans
 - Considering cost-effectiveness, affordability
 - And programmatic considerations, such as whether including such areas would simplify delivery

High priority M&E and research recommendations

- Immunological **co-administration studies** with other relevant infant vaccines such as pneumococcal conjugate vaccines, rotavirus, pentavalent vaccines (DTP-HepB-Hib), IPV, typhoid conjugate vaccine, meningococcal vaccine, hexavalent (DTwP-HepB-IPV-Hib) vaccine, measles vaccine, and observational studies for the occurrence of febrile seizures
- **Post-licensure evaluation studies should be conducted on vaccine effectiveness** in high perennial transmission settings, which are not represented in the Phase 3 trial
- **Monitoring for risk of malaria rebound** and collecting **further data on severe malaria and mortality** as part of the ongoing Phase 3 trial and 4 years of follow-up (already planned by the developer)

High priority M&E and research recommendations

- **Post-licensure monitoring of R21/Matrix-M safety in infants and young children**, including the occurrence of febrile seizures and mortality. Monitoring mortality may be most easily achieved in areas where there is a demographic surveillance system in place
- **Evaluation of vaccine efficacy against severe malaria** (e.g., case-control study)
- **Evaluation of vaccine impact on mortality using available systems** – e.g. HDSS, community mortality surveillance, case-control study
- **Interchangeability studies on heterologous schedules with RTS,S/AS01 and R21/Matrix-M**

WHO task team to help prioritize and monitor implementation and results of priority research

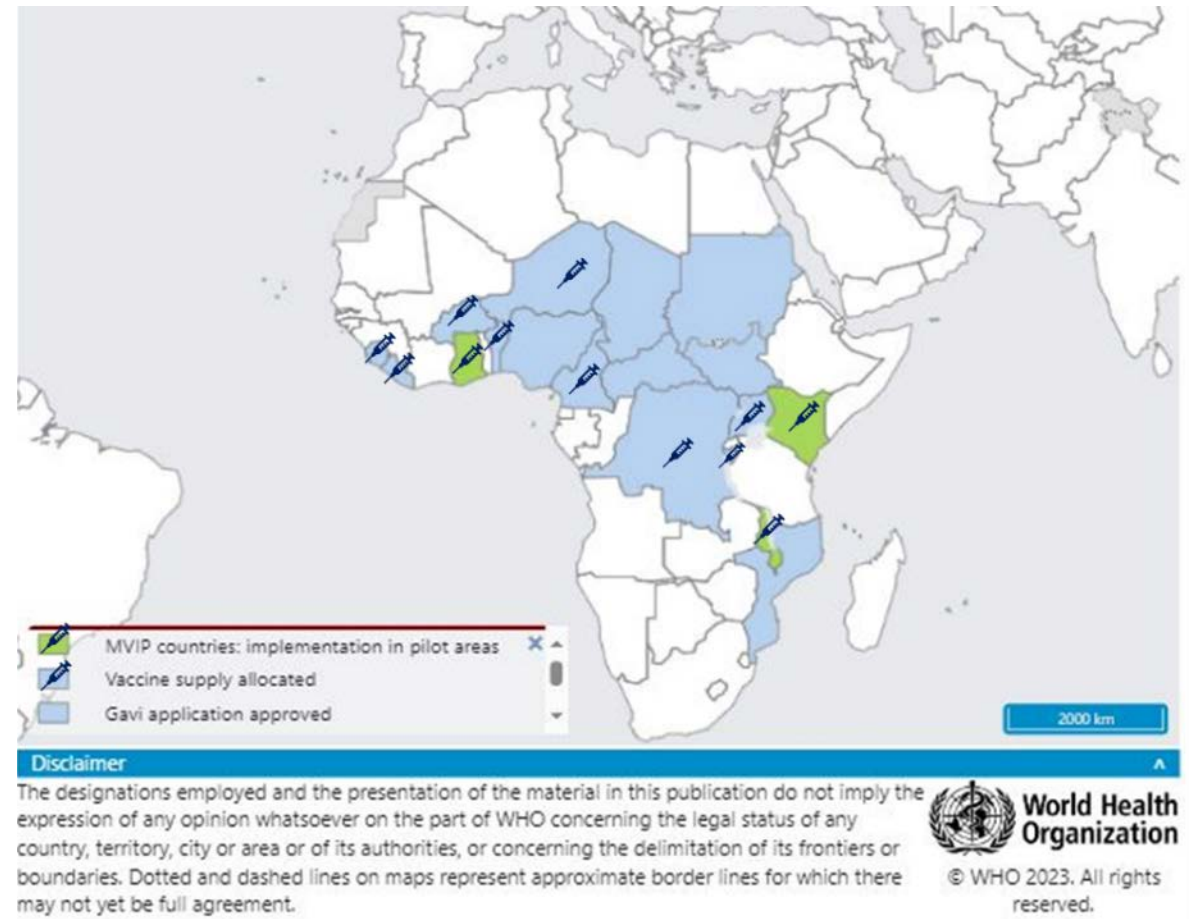
- SAGE and MPAG recommended a cross-department team (Immunization, Vaccines and Biological, Global Malaria Programme, Pharmacovigilance)
 - To help prioritize, coordinate and monitor identified high priority research activities
- Suggestion for development of generic protocols to guide study designs
- Terms of Reference for the cross-department team under development

Implications of R21/Matrix-M on malaria vaccine introduction in Africa

Eliane Furrer, WHO

Countries' Gavi application status for malaria vaccines - as of 28 Nov 2023

- **>30 countries** in Africa expressed interest in introducing a malaria vaccine
- Since opening the funding window in mid-2022, Gavi approved applications from 18 countries to introduce vaccine in routine immunization programmes:
 - **Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, DR Congo, Ghana, Kenya, Malawi, Niger, Nigeria, Liberia, Mozambique, Sierra Leone, South Sudan, Sudan, Uganda**
- In July 2023, first supply allocations confirmed for 12 countries (**in bold**) for introduction in Phase 1 (greatest need) areas based on Framework¹



Malaria vaccine supply availability

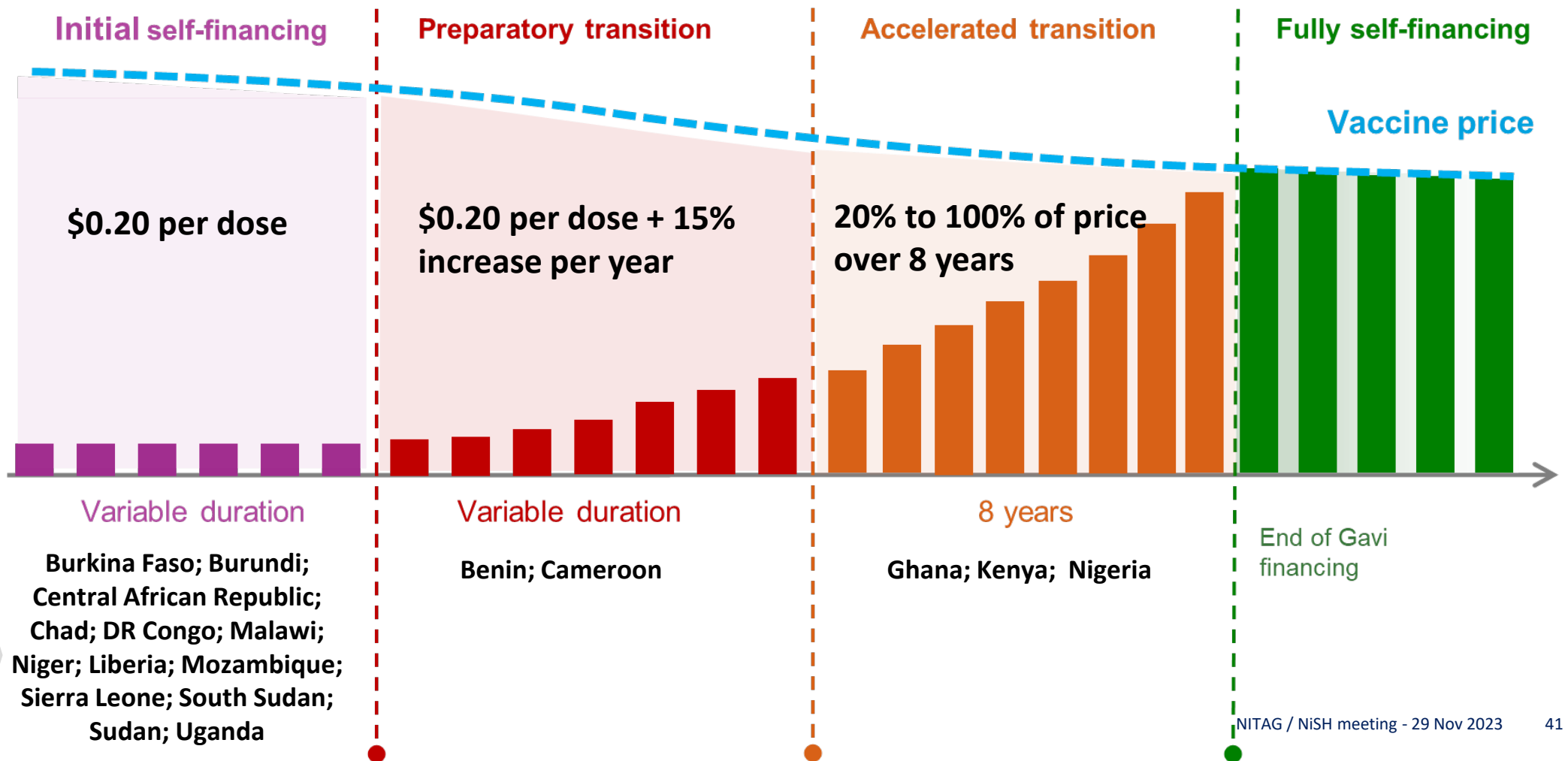
With appropriate planning, combined availability of RTS,S and R21 is expected to meet demand

| RTS,S/AS01 | Manufacturer | R21/Matrix-M |
|--|---------------------------|---|
| GlaxoSmithKline (GSK) | Market Pricing (2024) | Serum Institute of India (SII) |
| ~US\$10.00 per dose (EUR 9.30) | Price for country | US\$ 3.90 per dose |
| Dependent on Gavi eligibly status/ co-financing (see next slide) | Overall volumes available | Dependent on Gavi eligibly status / co-financing (see next slide) |
| <ul style="list-style-type: none">Limited overall supply of 18 million doses: 2023-25 → Intention: allocate to fewer countries to enable each country to scale up with the RTS,S doses availableTechnology transfer of RTS,S to Bharat Biotech is underway, with prospects of increased supply and reduced prices | | <ul style="list-style-type: none">Based on current estimated demand from countries, and subject to approximately four (4) months production lead time from confirmed order, UNICEF expects sufficient supply availability to meet countries' needs in 2024 and beyond as per WHO recommendations. |

Gavi co-financing: exceptional time-limited approach for malaria vaccines to facilitate affordability and uptake*

**To be reviewed no later than 2027*

As a country GNI per capita increases, the level of its co-financing rises




Co-financing status of countries with approved malaria vaccine application

Product information (as of November 2023)

Two malaria vaccines (RTS,S/AS01 and R21/Matrix-M) are recommended for use by WHO and available evidence indicates they are both safe and effective. The choice of product to be used in a country should be considered at a country level, based on the programmatic characteristics, vaccine supply, and affordability.

RTS,S/AS01

- Recommended by WHO since October 2021
- WHO PQ in July 2022
- To reduce *P. falciparum* malaria in young children living in areas where malaria is endemic, prioritizing areas of moderate to high transmission
- 4 doses: 3 monthly doses from 5 months of age and a 4th dose provided to prolong protection
- A 5th dose may be considered where there is a significant malaria risk remaining in children a year after receiving dose 4
- Two vials clipped together, reconstituted for 2 doses
- 2-8°C; 36 months shelf life
- 9.92 cm³ per dose (in secondary packaging)
- Good safety profile, robust safety database with about 5.8 million doses provided in pilot
- Associated febrile seizures
- About 6 million doses provided to 2 million children in pilot implementation in Ghana, Kenya and Malawi since 2019
- Phase 3 trial (2009-2014) in 11 sites in Africa across a range of transmission settings (low, mod, high or seasonal), 4 years follow-up; 7 years follow-up in 3 sites
- Phase 3 trial of seasonal malaria vaccination with or without seasonal malaria chemoprevention in 2 sites in Africa, 5 year follow-up.

 **WHO position**
PQ status

Indication
(per WHO recommendation)

Schedule
(per WHO recommendation)

 **Presentation**
Cold chain

Safety

 **Experience**
(Phase 3 and post-licensure)

R21/Matrix-M

- Recommended since October 2023
- WHO PQ under review; best case scenario: late 2023
- Same as RTS,S/AS01
- Same as RTS,S/AS01
- *Expected:* Single vial (liquid), 1 or 2 doses per vial (no reconstitution)
- 2-8°C; 24 months shelf life
- *Expected:* 7.03 cm³ per dose and 14.06 cm³ per dose (in secondary packaging, depending on presentation)
- Good safety profile, tested in Phase 3 trial (~4000 children).
- Associated febrile seizures
- Phase 3 trial in 5 sites in Africa (ongoing since 2021); As of October 2023, data available for 18 months follow up; data limited to low or low/mod settings, or highly seasonal settings

Next steps

- **Broader rollout of the RTS,S malaria vaccine is underway:** First vaccine shipment arrived in Cameroon, other countries to follow, for introductions starting in Q1 2024.
- **Ongoing introduction readiness preparations with countries in coordination with partners**
- **WHO pre-qualification review for R21/Matrix-M ongoing:** prerequisite for vaccine procurement by UNICEF for Gavi-eligible countries
 - Earliest expected arrival of R21/Matrix-M in countries: May –June 2024
- **For countries with approved application:**
 - **Product matching (for countries that have not confirmed RTS,S):** considering countries' product preferences, supply availability and overarching market shaping considerations
 - Countries invited by Gavi to submit requests for **scale-up** beyond Phase 1 areas → Incorporate the malaria vaccine into sub-national tailoring process
- **Additional countries** may apply to Gavi in future application windows (typically 4 times / year; next opportunity Jan 2024); non Gavi-eligible countries may access vaccine via UNICEF or directly from manufacturer

Key WHO technical resources

Available via the WHO Malaria Vaccines web site: [Immunization, Vaccines and Biologicals \(who.int\)](https://www.who.int/immunization/technical-resources)

And also on the TechNet-21 malaria vaccine site: <https://www.technet-21.org/en/topics/programme-management/malaria-vaccine>

And also on the WHO EPI site: <https://www.who.int/publications/m/item/essential-training-package-for-malaria-vaccine-introduction>



Full evidence reports for RTS,S/AS01 and for R21/Matrix-M

Incl. GRADE and Evidence to Recommendation Tables

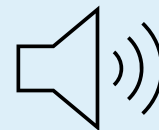


Generic training materials for health workers – for country adaptation



Guide for introducing a malaria vaccine into national immunization programmes

(advanced draft)



Communication and demand generation materials



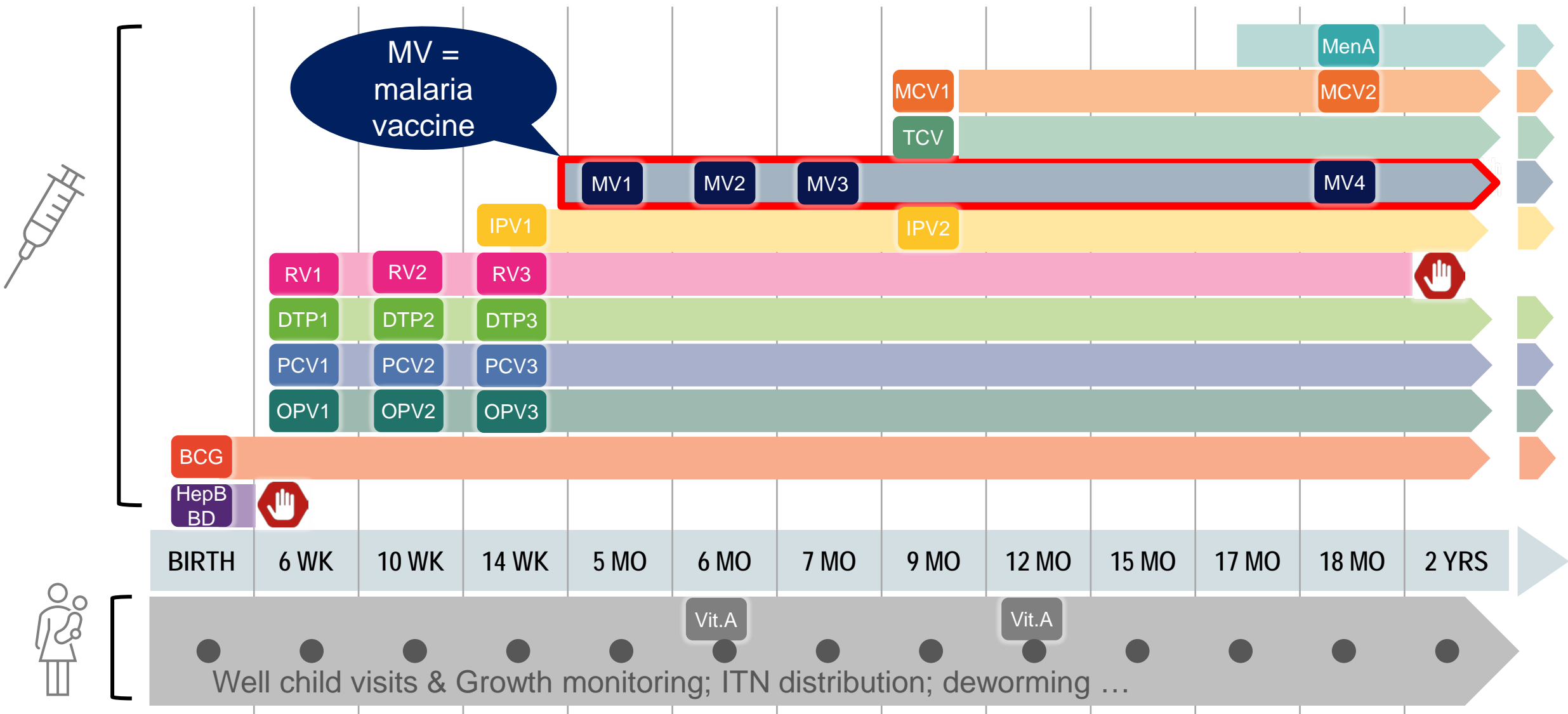
Introduction readiness assessment tool

Thank
you.



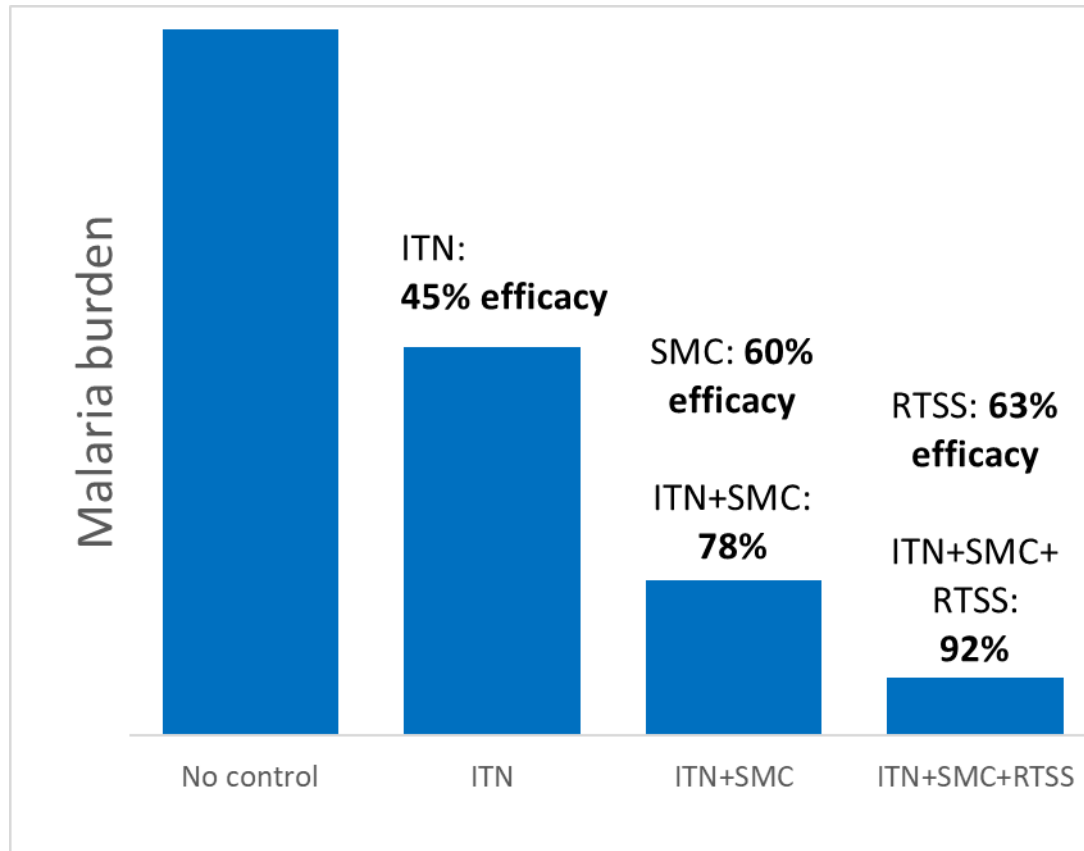
Back-up slides

Opportunities: leverage high demand to catch up on any missed vaccines or child health services through the 2nd year of life.



Highest impact achieved when malaria interventions strategically used together

Reduction in malaria burden when interventions are strategically used together



Insecticide Treated Net (ITN) efficacy:

<https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000363.pub3/full>

Seasonal Malaria Chemoprevention (SMC) efficacy:

85% per month, case control studies in 5 countries,
<https://journals.plos.org/plosmedicine/article/authors?id=10.1371/journal.pmed.1003727>
(SMC for 5 months covering 70% of annual burden)

RTS,S/AS01 efficacy of seasonal vaccination **39% efficacious over 3 years**

<https://www.nejm.org/doi/full/10.1056/NEJMoa2026330>