Schedule and delivery considerations for malaria vaccines in areas of seasonal transmission

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Credit: WHO/Neil Thomas.

Objectives

- To brief on the background of the RTS,S malaria vaccine and WHO recommendations
- To share WHO recommendations for malaria vaccine introduction in areas of highly seasonal malaria
- To share findings from trials comparing delivery options in areas of highly seasonal malaria
- To engage in a discussion of options for delivery of malaria vaccine in areas of highly seasonal malaria

WHO recommends the RTS,S/AS01 malaria vaccine be used for the prevention of *P. falciparum* malaria in children living in regions with moderate to high transmission as defined by WHO

World Health Organization

4-dose schedule

- First dose administered from 5 months of age
- Minimum interval of 4 weeks between doses
- 3-dose primary schedule
- 4th dose approx. 12 – 18 months after the 3rd dose to prolong duration of protection
- Flexibility in schedule to optimize delivery: to align the fourth dose with other vaccines given in the second year of life.
- Children who begin their vaccination series should complete the 4 dose schedule.

Countries may consider providing the vaccine seasonally, with a 5-dose strategy in areas with highly seasonal malaria or perennial malaria with seasonal peaks

- Seasonal vaccination to maximize impact by timing vaccination to the period of highest malaria transmission
- Primary 3-dose series provided monthly, additional doses provided annually prior to peak season (up to 5 doses total)
- Countries that choose seasonal deployment strategy strongly encouraged to document their experience

Product characteristics of WHO-prequalified RTS,S/AS01 malaria vaccine

Adjuvant AS01
liquid
(green ring)

Antigen RTS,S
lyophilized
(red ring)

Vials are clipped together to reduce the chance of reconstitution error

- Product overview on WHO list of pre-qualified vaccines: https://extranet.who.int/pqweb/content/mosquirix
- Injectable vaccine (intramuscular) consisting of two vials
- Once reconstituted, the vial contains TWO doses of vaccine (0.5mL/dose) which must be used within 6 hours or discarded at the end of the session, whichever comes first.
- Shelf life of 36 months at storage temperature between **+2°C and +8°C.** Freeze sensitive and light sensitive
- Vaccine Vial Monitor (VVM14)*
- Packing dimension of inner carton:
  - 100 vials (= 50 pairs, 100 doses) per pack
  - Volume : 9.92 cm^3/dose
- Co-administration: can be given concomitantly with Pentavalent (DPwP/Hep B/Hib), OPV, measles, rubella, yellow fever, rotavirus and pneumococcal conjugate vaccines

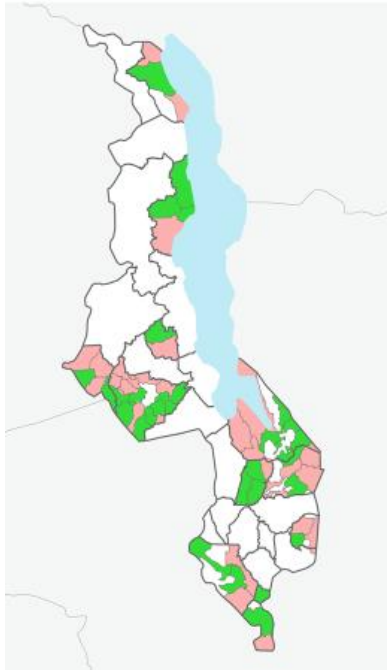
*VVM: label containing heat sensitive material registers cumulative heat exposure over time

Pilot implementations to understand the vaccine in routine use, (2019-2023)

Commitment to support continued vaccination in MVIP areas

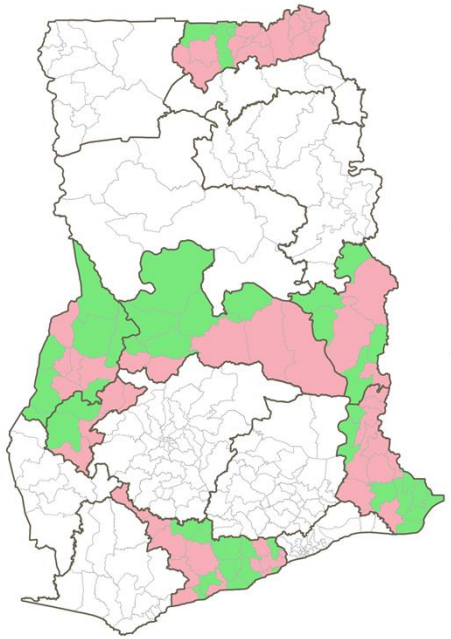
- Pilot vaccinating areas
- Pilot comparator (non-vaccinating) areas—following WHO recommendation will expand vaccination

Malawi



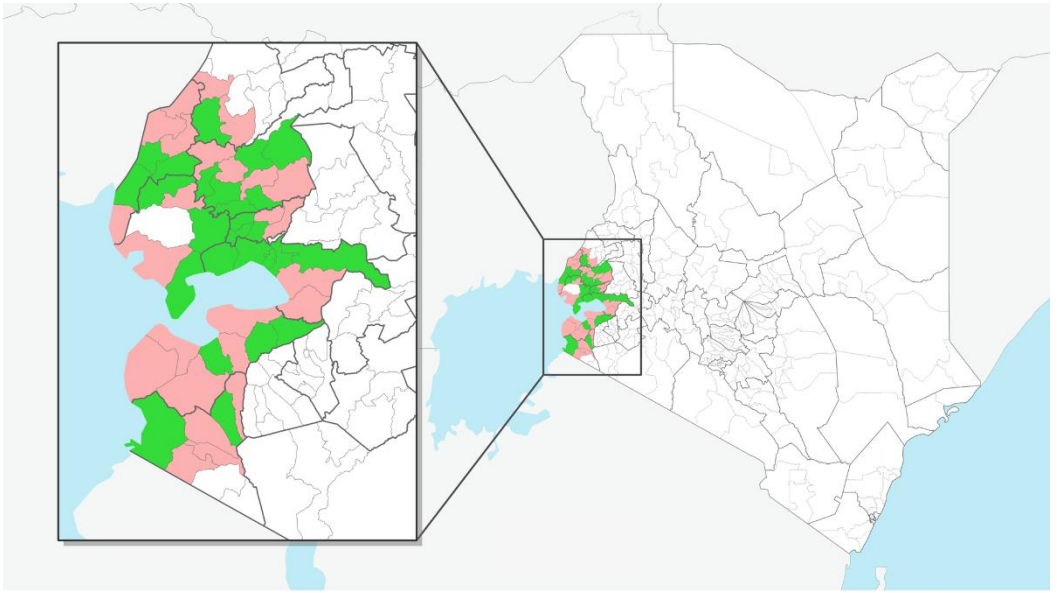
11 districts

Ghana



93 districts in 7 regions

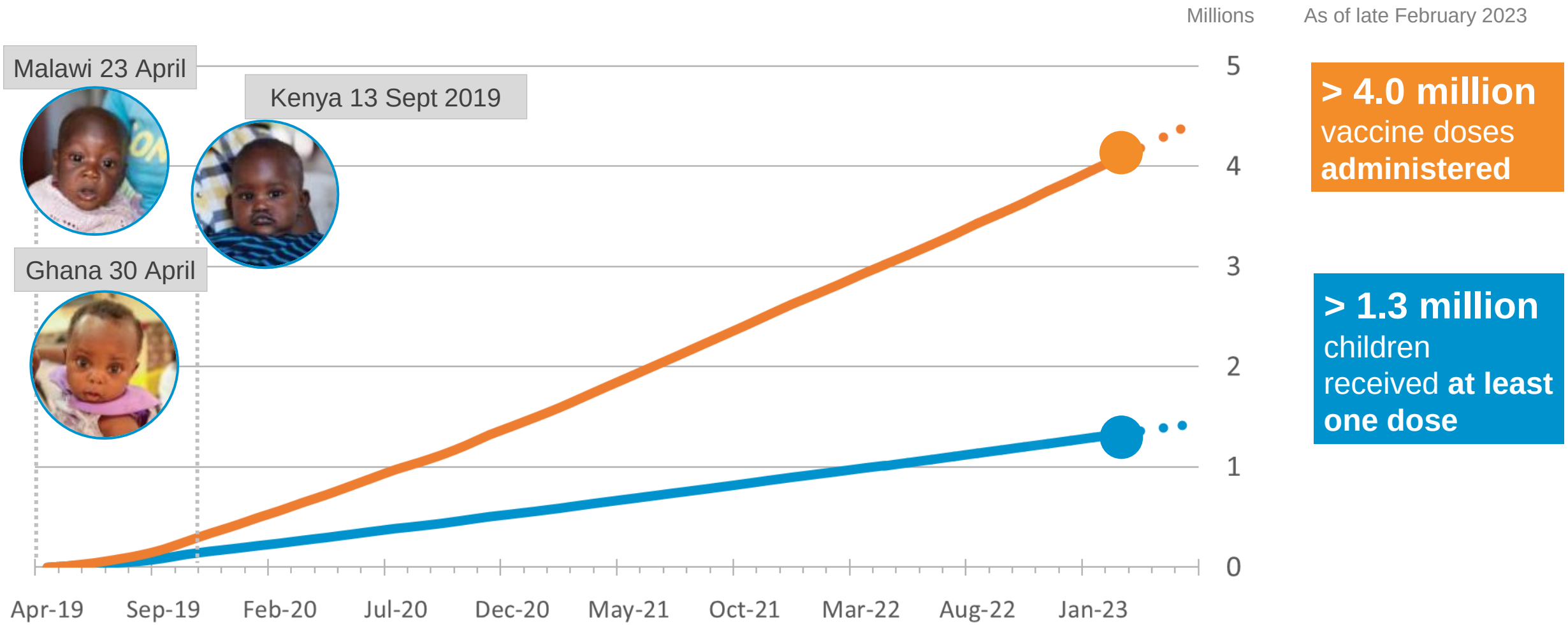
Kenya



51 sub-counties in 8 counties

Malawi and Ghana have expanded vaccination to the comparator areas: 27 November 2022 (Malawi); 20 February 2023 (Ghana); Kenya planning to commence in March 2023

Malaria vaccine implementation programme progressing well



Estimates as of February 2023, based on monthly MOH/EPI administrative data reports until December 2022 (for Kenya and Ghana) and September 2022 (for Malawi) and MVIP team projections for subsequent months

Summary findings from the MVIP: 24 months after first vaccination (April 2019 – April 2021)

1. **Feasibility:** Vaccine introduction is feasible, with good uptake and coverage through the routine systems, no impact on uptake of other vaccines, insecticide-treated bed nets (ITNs), care-seeking behavior
2. **Safety:** Vaccine is safe; no safety signals identified after over 3 million doses provided
3. **Impact:** Vaccine introduction resulted in a substantial reduction in severe malaria and all cause mortality in children age-eligible to receive the vaccine, even when introduced in areas with good ITN use and access to care
    - 32% (95% CI 8, 46%) reduction in hospitalized severe malaria
    - During 24 and 36 months after vaccine introduction, data show a reduction in all-cause mortality
4. **Equity:** the vaccine is reaching children who are not using other forms of prevention such as insecticide-treated nets, increasing access to malaria prevention interventions to >90%

WHO recommendation provides optional schedule for seasonal or 'hybrid' delivery

2022, 97, 61–80 No 9

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

4 MARCH 2022, 97th YEAR / 4 MARS 2022, 97e ANNÉE
No 9, 2022, 97, 61–80
http://www.who.int/wer

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Malaria vaccine: WHO position paper – March 2022

Introduction

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes. They summarize essential background information on diseases and vaccines and conclude with the current WHO position on the use of vaccines worldwide.

The papers have been reviewed by external experts and WHO staff and reviewed and endorsed by the WHO Strategic Advisory Group of Experts (SAGE) on Immunization (https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization). This paper has also been reviewed and endorsed by the WHO Malaria Policy Advisory Group (MPAG) (https://www.who.int/groups/malaria-policy-advisory-group). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) method was used to assess systematically the quality of the available evidence. The SAGE and MPAG decision-making process is reflected in "evidence-to-recommendation" tables. The processes followed for the preparation of vaccine position papers are described at: www.who.int/immunization/position_papers/position_paper_process.pdf. The WHO Global Malaria Programme follows the WHO guidelines development process described at: https://www.who.int/publications/i/item/9789241548960. The WHO guidelines for malaria are available at https://apps.magicapp.org/#/guideline/5700. The position papers are intended for use mainly by national public health officials and managers of immunization

Note de synthèse: position de l'OMS à propos du vaccin antipaludique – mars 2022

Introduction

Conformément à son mandat, qui prévoit qu'elle conseille les États Membres en matière de politique sanitaire, l'OMS publie une série de notes de synthèse régulièrement mises à jour sur les vaccins et les associations vaccinales contre les maladies ayant une incidence sur la santé publique internationale. Ces notes portent principalement sur l'utilisation des vaccins dans le cadre de programmes de vaccination à grande échelle. Elles résument les informations essentielles sur les maladies et les vaccins associés et présentent en conclusion la position actuelle de l'OMS concernant l'utilisation de ces vaccins dans le contexte mondial.

Ces notes ont été examinées par des experts externes et des membres du personnel de l'OMS, puis évaluées et approuvées par le Groupe stratégique consultatif d'experts (SAGE) de l'OMS sur la vaccination (https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization). Ce document a également été examiné et approuvé par le Groupe consultatif sur la politique de lutte contre le paludisme (MPAG) de l'OMS (https://www.who.int/groups/malaria-policy-advisory-group). La qualité des données disponibles a été évaluée de manière systématique au moyen de la méthode GRADE (Grading of Recommendations Assessment, Development and Evaluation). Le processus de décision du SAGE et du MPAG est reflété dans les tableaux des données à l'appui des recommandations. La procédure suivie pour élaborer les notes de synthèse sur les vaccins est décrite dans le document: www.who.int/immunization/position_papers/position_paper_process.pdf. Le Programme mondial de lutte contre le paludisme de l'OMS suit le processus d'élaboration des lignes directrices de l'OMS décrit dans le manuel disponible à l'adresse: https://www.who.int/publications/i/item/9789241548960. Les lignes directrices de l'OMS sur le paludisme sont disponibles à l'adresse: https://apps.magicapp.org/#/guideline/5542. Les notes de

61

Optional schedule for settings with highly seasonal malaria or perennial malaria with seasonal peaks

Countries may consider providing the RTS,S/AS01 vaccine seasonally, with a 5-dose strategy, in areas with highly seasonal malaria or with perennial malaria transmission with seasonal peaks. This strategy seeks to maximize vaccine impact by ensuring that the period of highest vaccine efficacy (just after vaccination) coincides with the period of highest malaria transmission. The primary series of 3 doses should be provided at monthly intervals, with additional doses provided annually, prior to peak transmission season. Countries that choose seasonal deployment of the RTS,S/AS01 vaccine are strongly encouraged to document their experience, including the vaccine effectiveness, feasibility and occurrence of any adverse events following immunization, to provide additional input for future updates to the guidance. WHO also encourages international and national funders to support relevant learning opportunities.

Schéma vaccinal optionnel pour les zones où la transmission du paludisme est fortement saisonnière ou permanente avec des pics saisonniers

Les pays peuvent envisager d'administrer le vaccin RTS,S/AS01 de façon saisonnière, avec une stratégie à 5 doses, dans les zones où la transmission du paludisme est fortement saisonnière ou permanente avec des pics saisonniers. Cette stratégie vise à maximiser l'impact du vaccin en faisant coïncider la période d'efficacité vaccinale la plus élevée (juste après la vaccination) avec la période de transmission palustre la plus forte. La série initiale de 3 doses doit être administrée en respectant des intervalles mensuels, et les doses supplémentaires fournies une fois par an, avant le pic de transmission saisonnière. Les pays qui choisissent le déploiement saisonnier du vaccin RTS,S/AS01 sont fortement encouragés à documenter leur expérience, notamment l'efficacité du vaccin en population, la faisabilité de la vaccination et la survenue de toute manifestation postvaccinale indésirable, afin de fournir des données supplémentaires pour les futures mises à jour de ces orientations. L'OMS encourage également les bailleurs de fonds internationaux et nationaux à soutenir ces possibilités d'apprentissage.

Vaccine efficacy when given using age-based strategy in perennial settings and using seasonal strategy in highly seasonal transmission settings

World Health Organization

Vaccine Efficacy: age-based strategy in perennial settings 2009-2014*

12 months follow-up	**3 doses**
VE against clinical malaria	**51%** (95% CI 47–55)
VE against severe malaria	**45%** (95% CI 22–60)
48 mths. (median) follow-up	**4 doses**
VE against clinical malaria	**39%** (95% CI 34–43)
VE against severe malaria	**29%** (95% CI 6–46)
VE against severe malaria anaemia	**61%** (95% CI 27–81)
VE against blood transfusions	**29%** (95% CI 4–47)
VE against malaria related hospitalization	**37%** (95% CI 24–49)

*booster dose given 18 months after the 3rd dose
*data shown are results for the 5-17 months age group

Efficacy from using the seasonal strategy Burkina Faso and Mali, 2021*

- **Seasonal vaccination non-inferior to 4 rounds of SMC in protecting against clinical malaria**
- **SMC prevents 75% of clinical and severe malaria cases****
- **Combined intervention of RTS,S and SMC is superior to either alone (comparison to SMC alone shown)**

CE against clinical malaria (primary end point)	**63%** (95% CI 58–67)
CE against WHO-defined severe malaria hospitalizations	**71%** (95% CI 42–85)
CE against severe malaria anaemia	**68%** (95% CI 34–84)
CE against blood transfusions	**65%** (95% CI 23–85)
CE against all cause deaths, excluding injuries and surgery	**52%** (95% CI 5–76)
CE against deaths from malaria	**73%** (95% CI 3–92)

- age: 5-17 months
- No evidence of safety signals seen in Phase 3 trial 2009-2014

Lancet. 2015 Jul 4;386(9988):31-45. doi: 10.1016/S0140-6736(15)60721-8. Epub 2015 Apr 23

*Chandramohan *et al*, N Engl J Med 2021; 385:1005-1017; DOI: 10.1056/NEJMoa2026330
** WHO policy recommendation SMC, 2012

Schedule considerations

Minimum age for 1st dose, no maximum	Eligibility is based on a minimum of 5 months of age at 1st dose
No maximum age for final dose	A child may receive dose 4 at any age. Practically, immunization programmes may choose to offer late vaccination until 5 years.
Scheduling late doses	If child presents late, they should be given the dose due. Minimum interval between doses is 4 weeks. Following late vaccination, assess when the next malaria vaccine dose comes in the EPI schedule: 1. If more than 4 weeks away, the child should return at the regularly scheduled time point (e.g., X months of age) 2. If less than 4 weeks away, the child should return after minimum interval (4 weeks)

Schedule considerations

- Best protection is after **completion of the primary series** (3 doses)

For age-based delivery:

- Dose 4 given at **15 months of age** may have programmatic benefits if other 2YoL vaccines are given then
  - e.g, Increasing coverage for other 2YoL vaccines and provide an opportunity for catch-up vaccination
  - MVIP experience showed that it has been hard to achieve high coverage at 24 months of ages

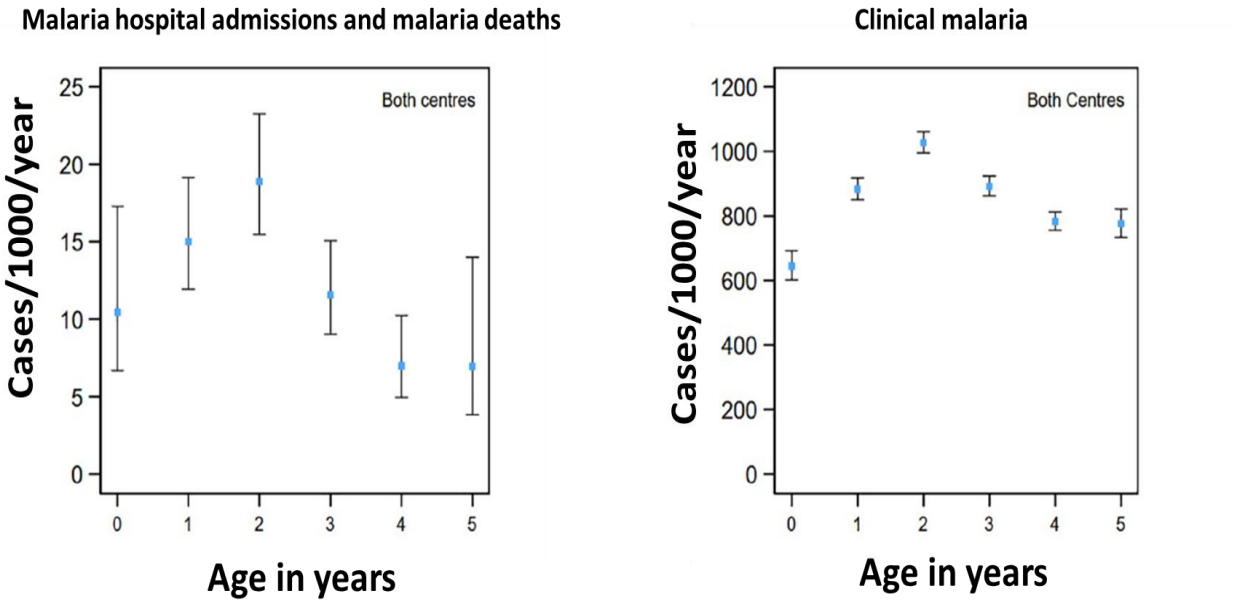
BUT, consider implications for **duration of protection**:

- Immune response reaches its highest after dose 3 and then wanes before dose 4
- Duration of protection may not last as long through high-risk period (up to around 3 years of age) compared to giving the 4th boost dose at **18 or 24 months**

- **Dose 4 at 18 months of age may provide the best opportunity to align with other 2YoL vaccines, but scheduling closer to 2 years of age prolongs protection**

Risk of malaria disease and death

Incidence of malaria in cohorts of children with high SMC coverage in the AZ-SMC trial, Burkina Faso and Mali, 2014-2016



Chandramohan et al., NEJM, 2019; Cairns et al., PLOS Med 2020

AZ-SMC trial, Burkina Faso and Mali 2014-2016, (Chandramohan et al., NEJM, 2019):

https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003214

- ~40% of clinical cases above 3 years of age
- ~30% of malaria hospital admissions above 3 years of age
- ~20% of malaria deaths above 3 years of age

MVIP:

Areas without RTSS.; Severe malaria under 5 yrs, **% aged 3-4yrs**:

- Ghana **31%**
- Malawi **22%**
- Western Kenya **29%**

(credit: Paul Milligan)

Malaria vaccine integration with other vaccines, malaria interventions, or health services

Category	Intervention
Commodities and treatment	Anti-helminthic treatment (de-worming)
	Vitamin A supplementation
	LLINs for malaria control (reminders/ campaigns)
	Growth monitoring
	Iron and folic acid supplementation
	Perennial Malaria Chemoprevention (PMC)-(children <1 year of age) - **screening**, **providing catch-up/missed doses**
	Seasonal malaria chemoprevention (children <5 years of age) - **(vaccination referrals/reminders during SMC campaigns)**
Information and life skills	Education on the prevention and treatment of malaria
Other vaccines	Opportunities may be found with: • Measles second dose , MenA, TCV (**18 or 15 month visit**, malaria vaccine 4th dose) • Measles first dose, yellow fever, IPV MenA, TCV (**9 month visit**) • School-based vaccination strategies for 2YoL

Considerations for malaria vaccination strategies in areas with highly seasonal malaria transmission

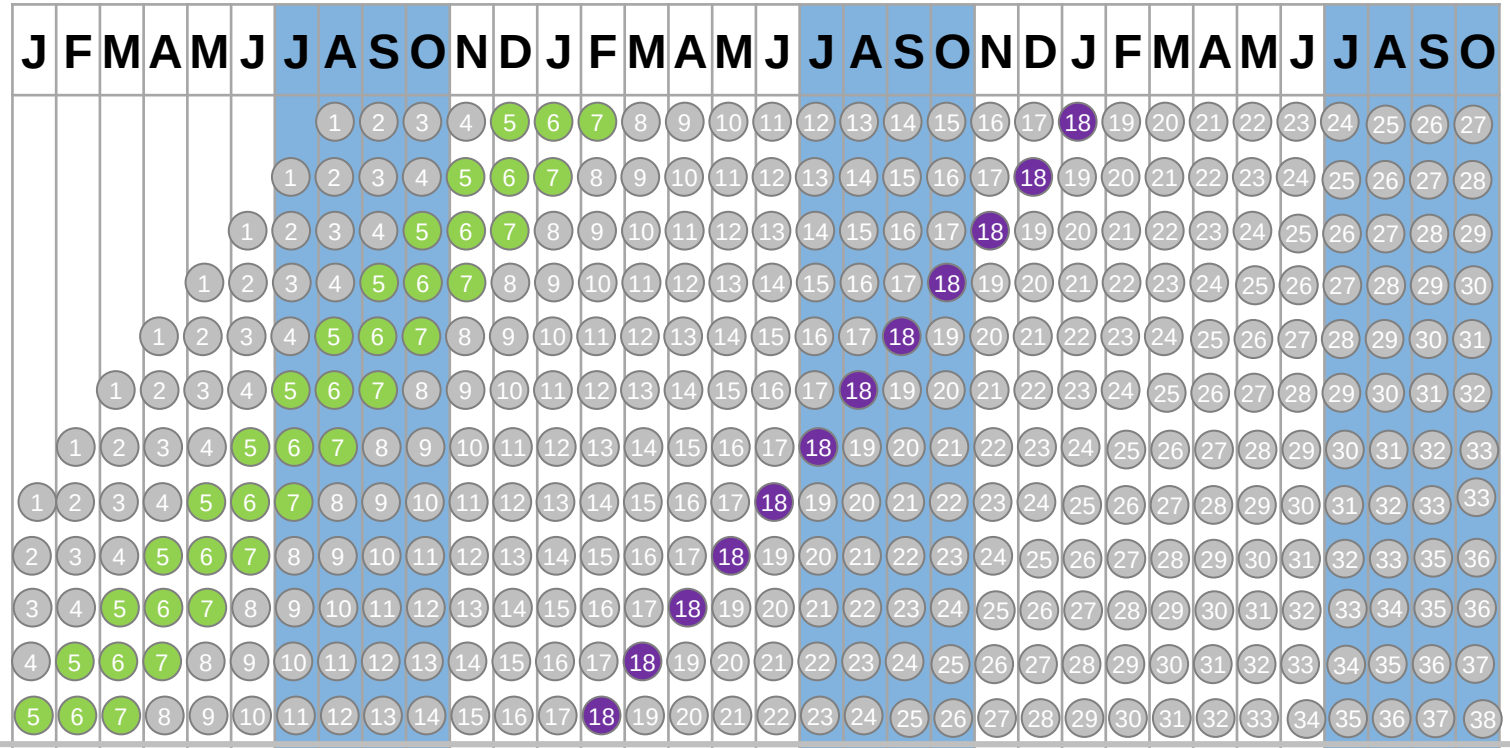
- **Campaign style delivery (timed doses to the high malaria transmission season)**
  - Primary doses (3-doses) given prior to the peak transmission season followed by additional annual doses, also given before the peak transmission season (5-dose strategy or >5 doses?)

- **Hybrid-approach-**[WHO has initiated consultations with technical advisory bodies to provide implementation guidance]
  - Primary doses (3 doses) delivered through the routine EPI (age-based) with the annual doses (seasonal boost) given through a **vaccination campaign** prior to the peak transmission season
  - Primary doses (3 doses) delivered through the routine EPI (age-based) with the annual doses (seasonal boost) given through a **media campaign/intensified communication** **(doses delivered using routine EPI delivery platform, e.g., static, outreach)** prior to the peak transmission season

- **Routine delivery through the EPI (static, outreach, camp-out etc.)**
  - Age-based delivery through the EPI using 4-dose schedule (e.g., 5,6,7,18 mths; 5,6,7,15 mths; 6,7,8,15 mths; 6,7,8,18 months)
  - Age-based delivery through the EPI using 4-dose schedule with timed/seasonal PIRIs/catch-up (prior to the peak transmission season)

Considerations on schedule strategies (age-based)

Routine delivery (4-dose schedule) Option 1
(all doses in routine EPI)
5,6,7, 18 months schedule



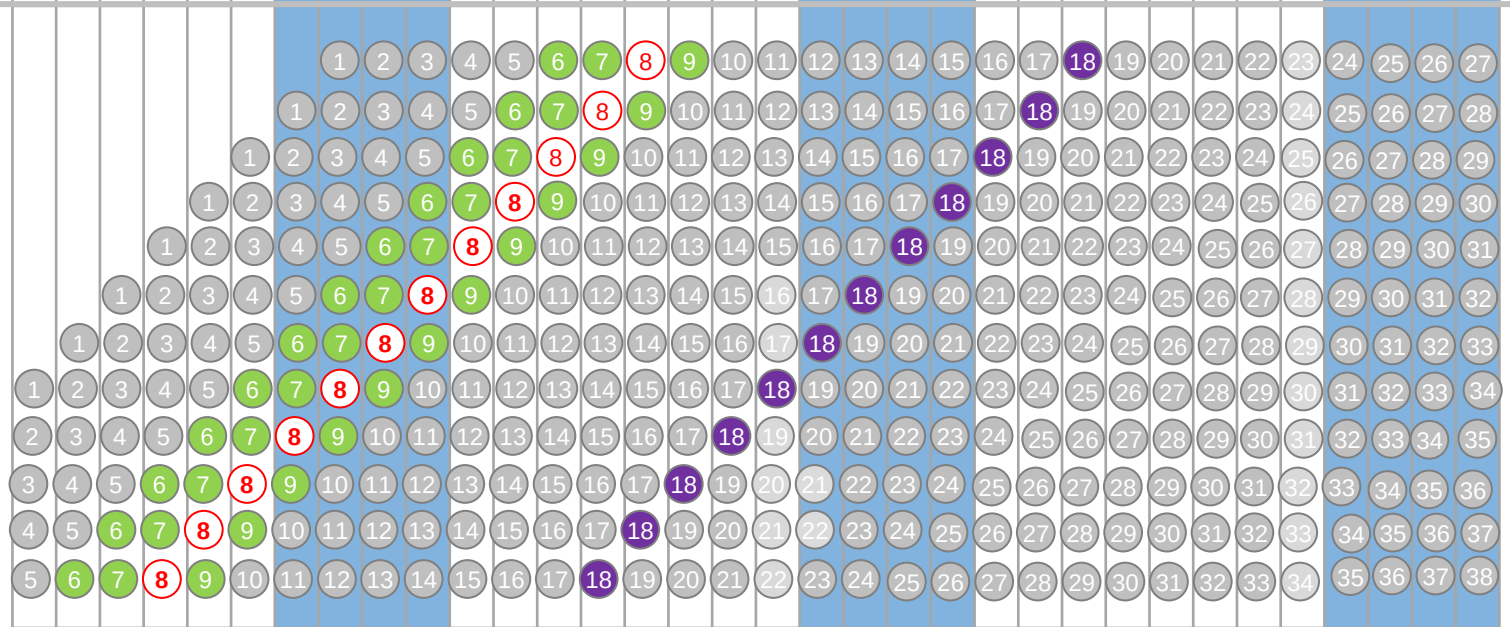
3-dose primary series

Dose 4

Peak malaria transmission season

Option of conducting seasonal PIRIs/catch up (before the peak transmission season)

Routine delivery (4-dose schedule) Option 2
(all doses in routine EPI)
6,7,9 18 months schedule

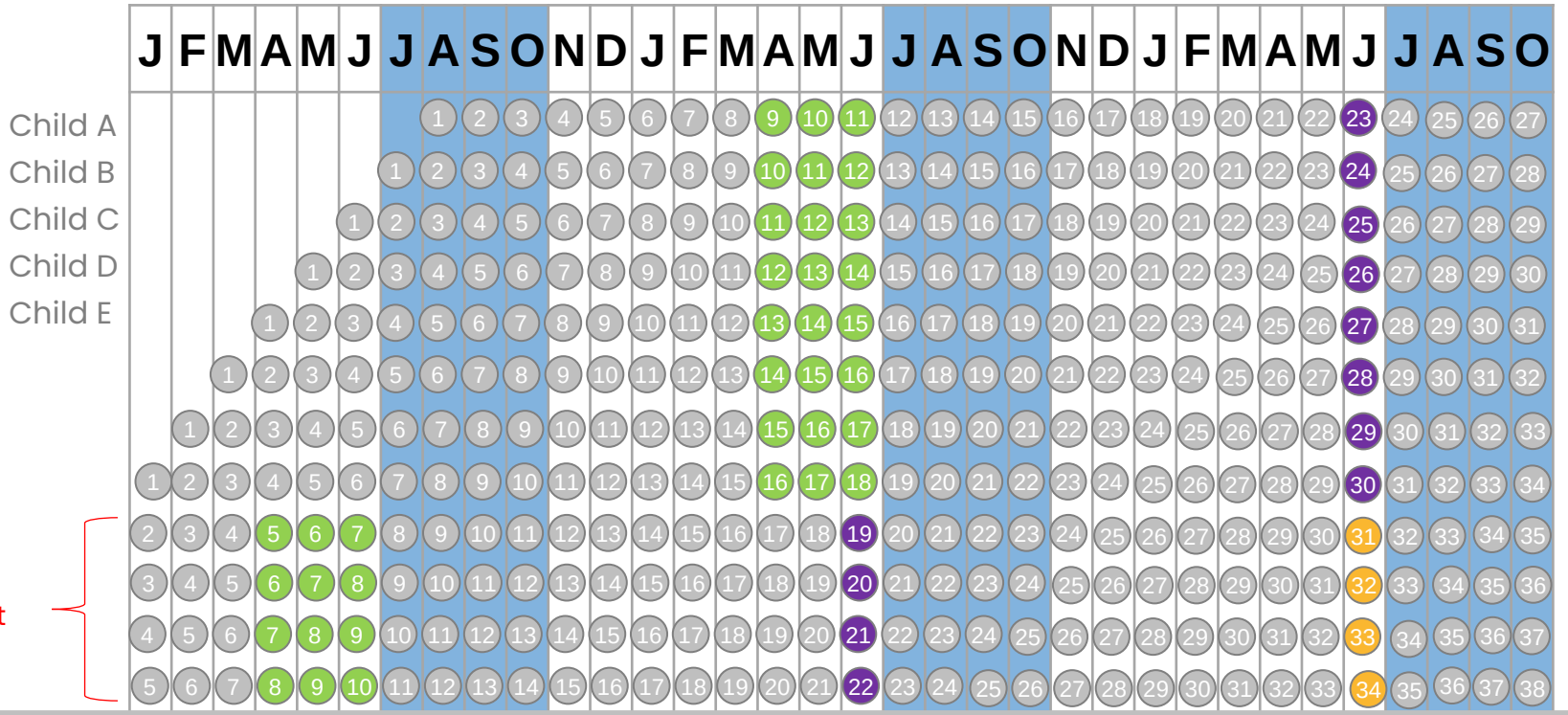


Countries may consider aligning 3rd dose with existing vaccination visits:

- Eligibility may be confusing for healthcare workers as observed in the pilots and lead to missed opportunities
- Increased risk: some children may not complete primary series before high transmission season

Considerations on schedule strategies for seasonal dosing

Campaign Delivery Option ("e.g. campaign" starting in April from **age 5 months**)



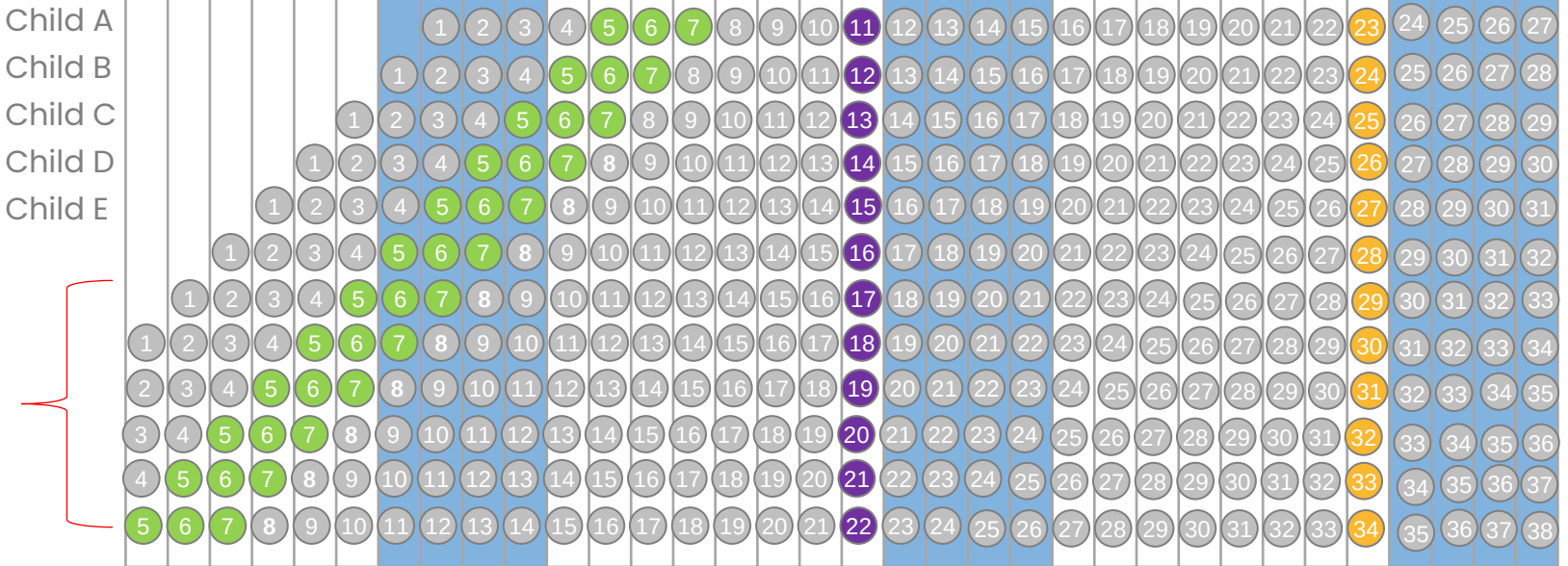
3-dose primary series

Dose 4

Dose 5

Peak malaria transmission season

Hybrid Delivery Option (initial 3 doses in routine EPI) 5,6,7 months and annual seasonal doses through campaign or intensified communication



With the hybrid approach;
Annual doses can be delivered:

1. Through a vaccination campaign
2. Intensified communication/media campaign and vaccines delivered through the routine EPI platform

Pros and cons for the different delivery strategies

Delivery strategy	Pros	Cons
Routine delivery through the EPI		
Age-based delivery through the EPI using 4-dose schedule	❑ Delivery through a well-known and established system and opportunity to strengthen RI ❑ Relatively simple messaging of the schedule & age eligibility ❑ Caregivers and HCWs may be more familiar with this strategy ❑ Comparatively less resource-intensive than a campaign style delivery	❑ High dropout rate between doses ❑ Relies on well-functioning EPI and health delivery system to achieve good coverages ❑ Potential challenges with 4th dose coverage ❑ Sub-optimal protection for some children given timing of administration in relation to the peak transmission season
Age-based delivery through the EPI using 4-dose schedule with timed/seasonal PIRIs/catch-up (before the peak transmission season)	❑ Provides opportunity to catch up on other vaccines or interventions ❑ Has the potential to reduce dropout rates with good 4th dose coverage compared to "regular" routine delivery	❑ Need for resources to sustain PIRIs ❑ *other potential challenges as above*
Campaign style delivery	❑ Has the potential to reach high coverage for all doses ❑ Leverages the period of high vaccine efficacy vs. high malaria transmission and thus provides greater protective efficacy ❑ May be suitable for specific populations (difficult to reach with poor health service delivery)	❑ Resource intensive ❑ May disrupt provision of other essential health services if not properly integrated and planned (vaccination campaigns and SMC) ❑ Messaging and communication of the target age group may be complicated

Pros and cons for the different delivery strategies

Delivery strategy	Pros	Cons
Hybrid-approach		
Primary doses (3 doses) delivered through the routine EPI (age-based) with the **annual doses (seasonal boost) given through a vaccination campaign** before the peak transmission season	❑ Primary doses delivered through an established platform ❑ Timed annual doses before the peak malaria transmission doses for children who have completed primary series provides greater protective efficacy	❑ Potential of poor coverage of primary doses if EPI delivery system is suboptimal ❑ Vaccination campaign may require sustainable financing ❑ Variable interval between 3rd and 4th dose **vs.** current guidance
Primary doses (3 doses) delivered through the routine EPI (age-based) with the **annual doses (seasonal boost) given through a media campaign/intensified communication (using routine EPI delivery)** before the peak transmission season	❑ Advantages mainly same as above in addition to providing the opportunity to integrate and optimise delivery with other child health interventions through the media campaigns	❑ Need for sustainable funding to ensure effective community mobilization through media campaigns ❑ May not be the best strategy for difficult to reach populations (will require extensive outreach services, if this is planned to be HF-based) ❑ May result in low coverages and drop-out if media campaigns are not effective ❑ Variable interval between 3rd and 4th dose vs. current guidance

What is the best schedule for my country?

Issues to consider:

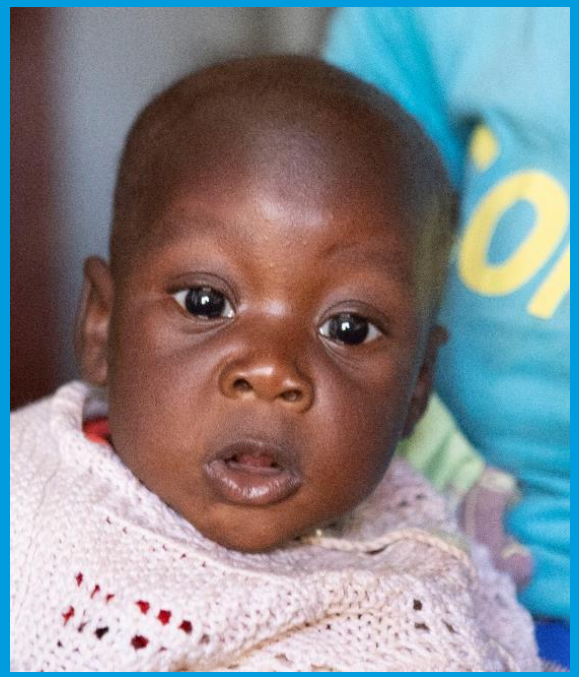
- Epidemiology / burden
  - At what age do children begin getting sick from malaria?
  - In highly seasonal areas, how to ensure most children protected before peak transmission season
- Vaccine efficacy & waning of protection
  - VE is highest after 3 doses
  - Waning of VE in relation to the interval between dose 3 and 4
- Likelihood of reaching high coverage (=> effectiveness => impact)
- Programmatic implications (positive and negative) of additional visits, for example:
  - Opportunities for integration with other interventions
  - Multiple injections at a single visit
  - Opportunities for catching up on previously missed doses or correct backsliding
  - Burden on caregivers
- Ease of communication to health workers and care-givers

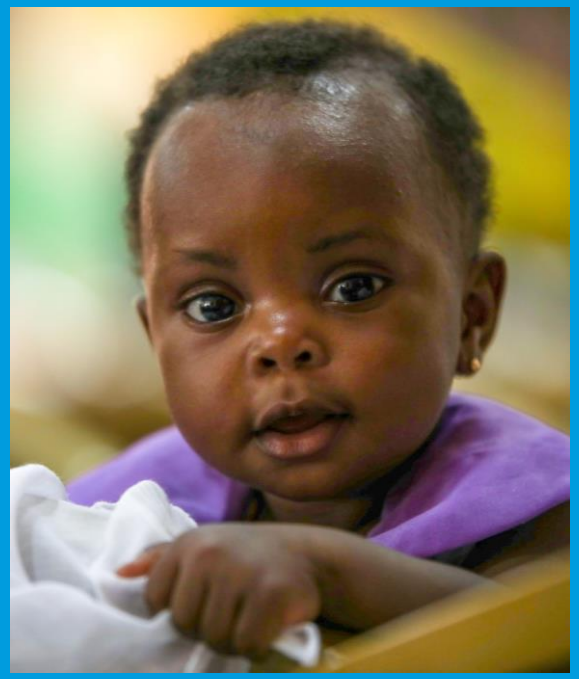
Outstanding questions

- What is the optimal interval between dose 3 and 4?
  - ➢ WHO and partners supporting modeling studies
- What should be the target age group for the campaign style delivery?
  - ➢ Consider VE in younger children <5 months and older children >17 months
  - ➢ Context of limited supply in the initial phase of the vaccine roll-out
- Additional annual doses:
  - ➢ Safety and efficacy of >5-dose strategy?
- What is the best delivery strategy depending on the malaria transmission intensity and length of the transmission season?
- Optimizing delivery through integration with other health interventions

Current evidence and recommendations

- Current WHO Position based on clinical trial data from:
  - ➢ Aged-based strategy in a perennial transmission setting -
    - "The vaccine should be administered in a 3-dose primary schedule, with a fourth dose provided approximately 12–18 months after the third dose to prolong the duration of protection. However, there can be flexibility in the schedule to optimize delivery, for example, to align the fourth dose with other vaccines given in the second year of life" (WHO Position Paper)
  - ➢ Campaign strategy in highly seasonal transmission settings (leveraging period of high vaccine efficacy)- (5-dose strategy) Chandramohan et al, N Engl J Med 2021; 385:1005-1017; DOI: 10.1056/NEJMoa2026330
- Seasonal malaria vaccination is a new area with outstanding questions to answer on delivery strategies, optimal number of annual doses, vaccination schedule etc.
- It is highly recommended that countries document lessons learned when the choose seasonal vaccination especially on operational feasibility, vaccine efficacy and safety.





Temps pour des questions
Any questions?