ARVAC 2023: The challenge of malaria vaccines

Dr. Mary Hamel, Team Lead Malaria Vaccines, IVB, WHO

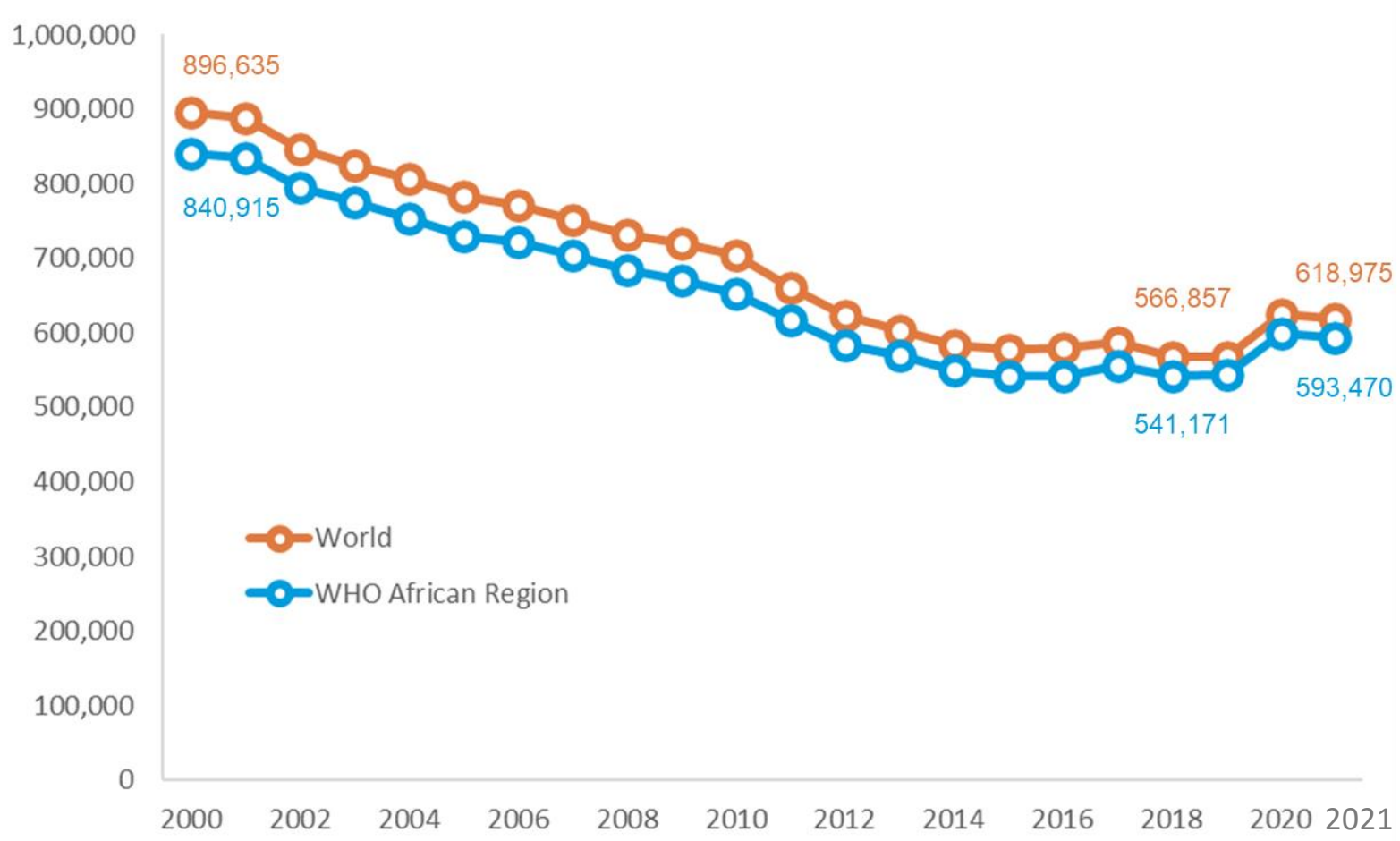
Agenda

1. The challenge of malaria vaccine development
2. The challenge of the first malaria vaccine, RTS,S/AS01
3. The challenge of meeting high demand with limited supply
4. The challenge of bringing a vaccine targeted to LMIC through development to delivery

Malaria continues to be a major cause of childhood morbidity and mortality, particularly in Africa

World Health Organization

Global trends in malaria deaths, 2000–2021



Global Trends (2021)

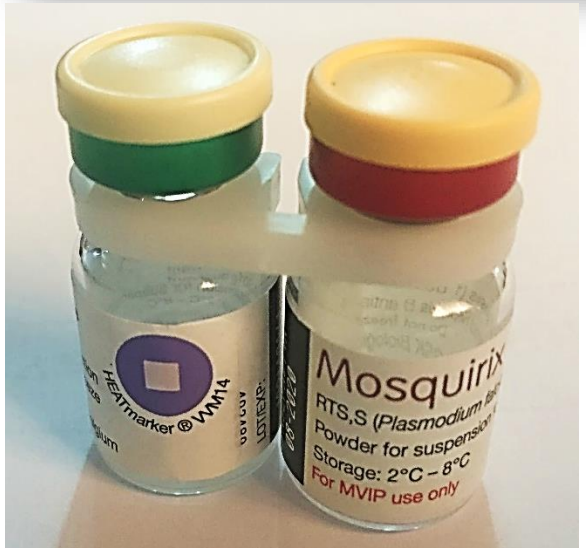
- 247 million cases
- 619 000 deaths

Highest Burden in Africa

- 95% of all cases and 96% of all deaths
- **468 000 child deaths**

Source: World Malaria Report 2022

Malaria prevention: layering malaria prevention interventions for increased impact



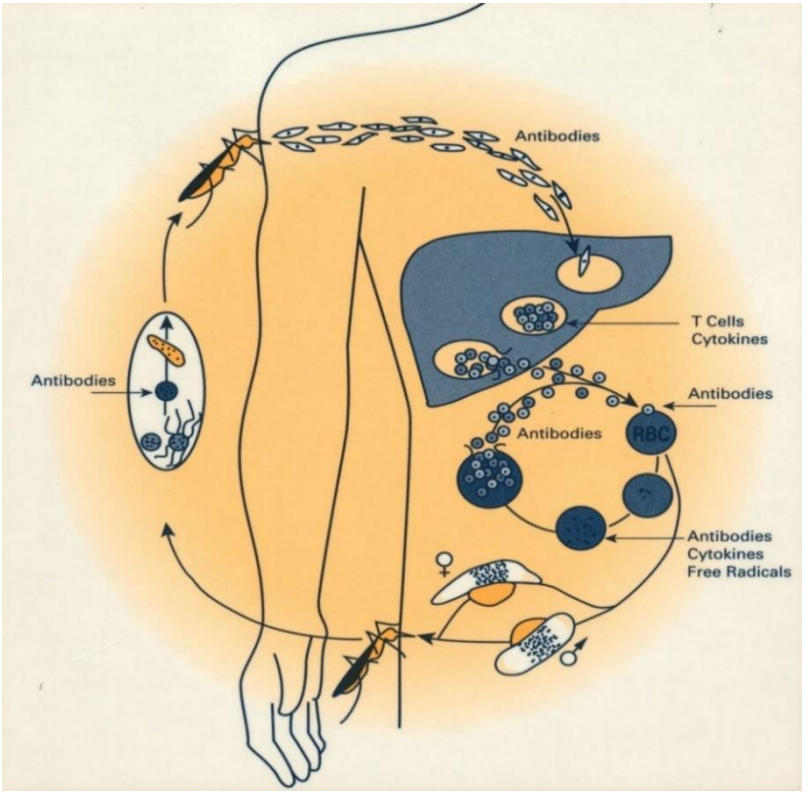
The addition of the malaria vaccine to current control tools could change the trajectory of malaria burden and result in an estimated 40K-80K lives saved yearly

World Health Organization

The challenge of malaria vaccine development

60+ yrs – the challenge of malaria vaccine development

- Complex parasite with over 5000 genes
  - large proportion devoted to immune evasion
  - In nature, parasite efficiently establishes repeated new and chronic clinical and sub-clinical infections
  - Multiple parasite stages; multiple strains
  - Multiple antigens, high antigenic variation
- Immune response
  - Acquired immunity is stage-specific and strain-specific (with cross-reactivity)
- Vaccine development challenges
  - No validated correlates of protection
  - Human challenge model, important addition
  - Variable correlation with field efficacy
  - Costly clinical development pathway with little incentive to manufacturers (lack of high-income market)



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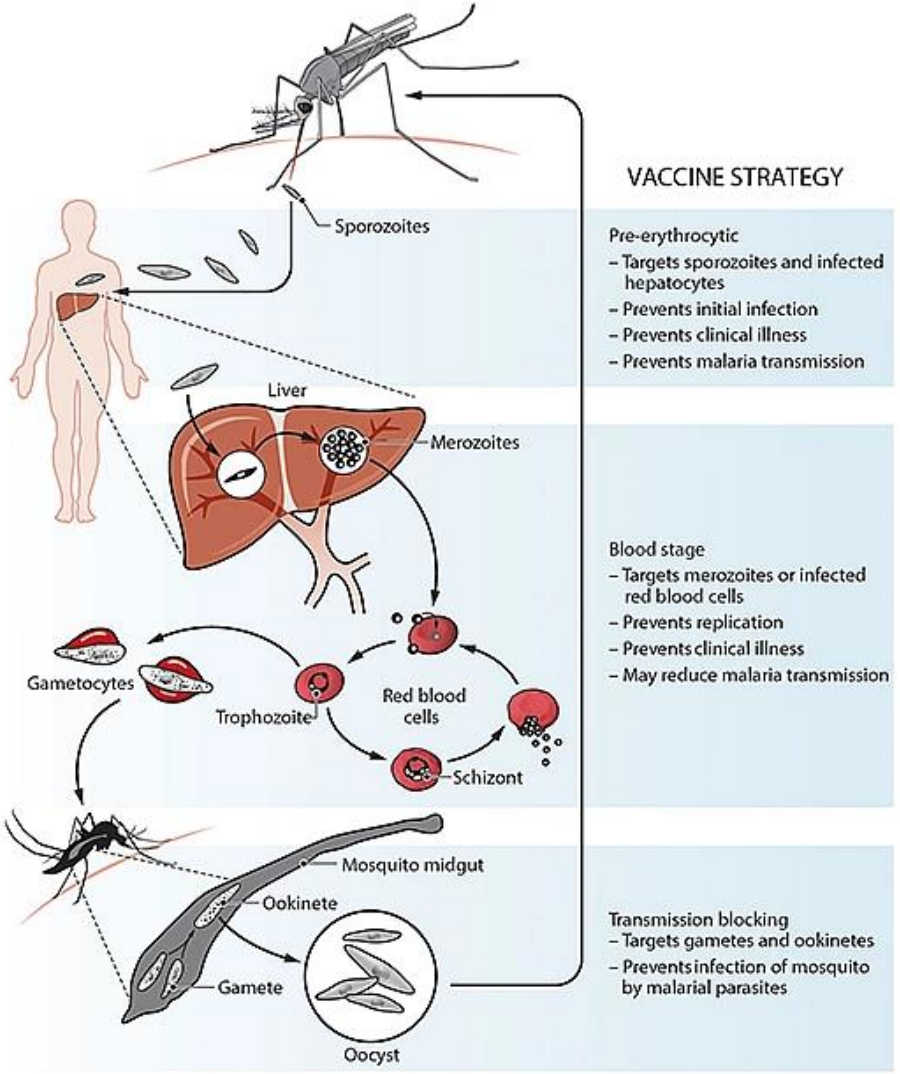
Malaria vaccine targets and strategies



Recommended vaccine: RTS,S/AS01
Under review: R21/MatrixM

Source: *Beeson et al, Science Translational Medicine 2019*

World Health Organization

Candidate vaccines in advanced clinical development

Recommended vaccine: RTS,S/AS01

Pre-erythrocytic (*P. falciparum*) candidates:

- **RTS,S/AS01 pre-erythrocytic (phase 4)**
  - Phase 3: fractional dose, seasonal vaccination
- **R21 Matrix-M (phase 3)**
  - Anti-sporozoite subunit vaccines
- **PfSPZ Vaccine (phase 2)**
  - Whole sporozoite (radiation attenuation)
- **PfSPZ CVac (phase 2)**
  - Whole sporozoite (chemically attenuated) with chemoprophylaxis
- **BNT165b1 – mRNA vaccine (phase 1, first in human)**
- rCSP (full length) subunit (phase 1)
- FMP013/FMP014 self-assembling nanoparticle (phase 1, ongoing)
- VLPM01 virus-like particle (phase 1, 2020), DNA ChAd63 PfCSP PfAMA1 ME-TRAP (phase 1, 2020), GAP genetically attenuated whole sporozoite vaccine (phase 1, 2019), ChAdOx1 MVA LS2 (phase 1, 2017), PfAMA1 (phase 1, 2015)

Blood stage (*P. falciparum*)

- **Rh5 (phase 2a, 2019)**
  - Reticulocyte-binding protein homologue 5
- SE36 (formerly BK-SE36) (phase 1, 2020)
- CAP chemically attenuated whole parasite (phase 1, 2018)
- GMZ (phase 1, 2016), P27A synthetic peptide (phase 1, 2015)

Sexual stage / transmission blocking (*P. falciparum*)

- Pre-fertilisation - **Pfs230 (phase 2, 2020)** and Pfs48/45
- Post-fertilisation – **Pfs25 (phase 2, 2020)** and Pfs28

P. vivax (phase 1/2a)

- PvDBP (phase 2, ongoing) – blood stage duffy-binding protein
- Pvs25 (phase 1, ongoing) - sexual-stage protein vaccine
- PvCSP (phase 2, ongoing)
- PvSPZ (phase 2a, 2017) - irradiated sporozoites

Malaria in pregnancy

- Two VAR2CSA antigen-based vaccines currently in phase 1
  - PRIMVAC (phase 1, 2019) and PAMVAC (phase 1, 2017)

Credit: WHO/M.Nieuwenhof

The challenge of the first malaria vaccine, RTS,S/AS01

The RTS,S/AS01 malaria vaccine: 30+ years of development

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2015
EMA positive scientific opinion granted

2016
WHO recommendation for pilot implementation: ***feasibility of delivery, safety, impact***

Oct 2021
WHO recommends broad use

Dec 2021
Gavi Board decision to fund RTS,S vaccine roll-out

2022, 2023
Gavi IRC reviews and approves first applications

Discovery | Pre-clinical | Phase 1 | Phase 2 | Phase 3 | **Malaria Vaccine Implementation Programme 2017-2023** | Vaccine Roll-out

1984
GSK team established to find a malaria vaccine

1987
WRAIR & GSK Candidate vaccine with immune response

1995
First clinical trials in adults begin in US, followed by trials in adults in Africa

2004
Proof of concept demonstrated in African children, then in infants

2009
Phase 3 trial in 11 sites in 7 African countries

2015
Phase 3 final results published

2019
National Regulatory Approval; Vaccine launch in routine programme in Ghana, Kenya, Malawi

2021
Pilot evaluations 24-month analysis on safety and impact

2024
First vaccine introductions outside of pilot areas

Pilot phased introduction sub-nationally with rigorous evaluation through sentinel hospital and community-based mortality surveillance

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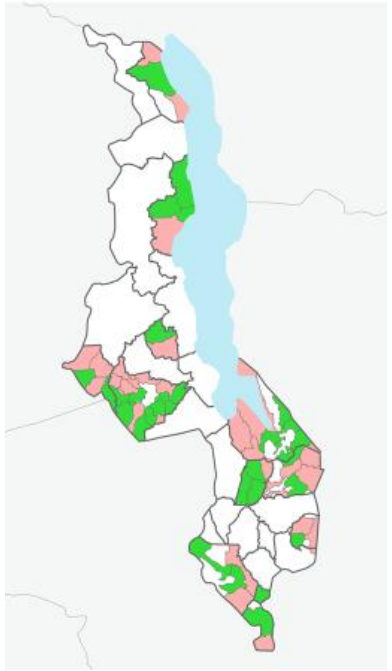
Malawi

First introduced: 23 April 2019

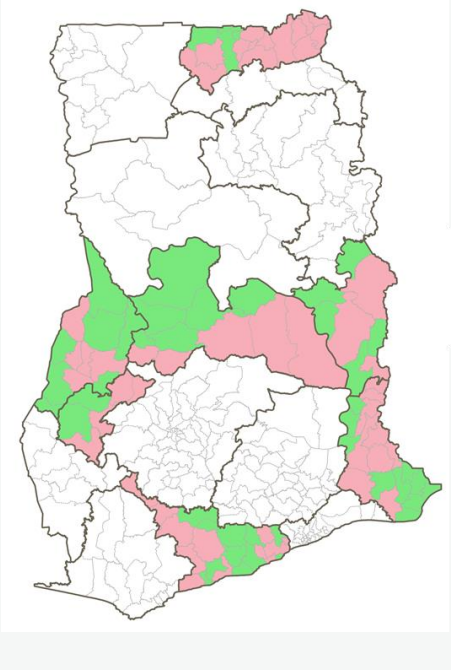
Expanded: 29 Nov 2022



Ghana

First introduced: 30 April 2019

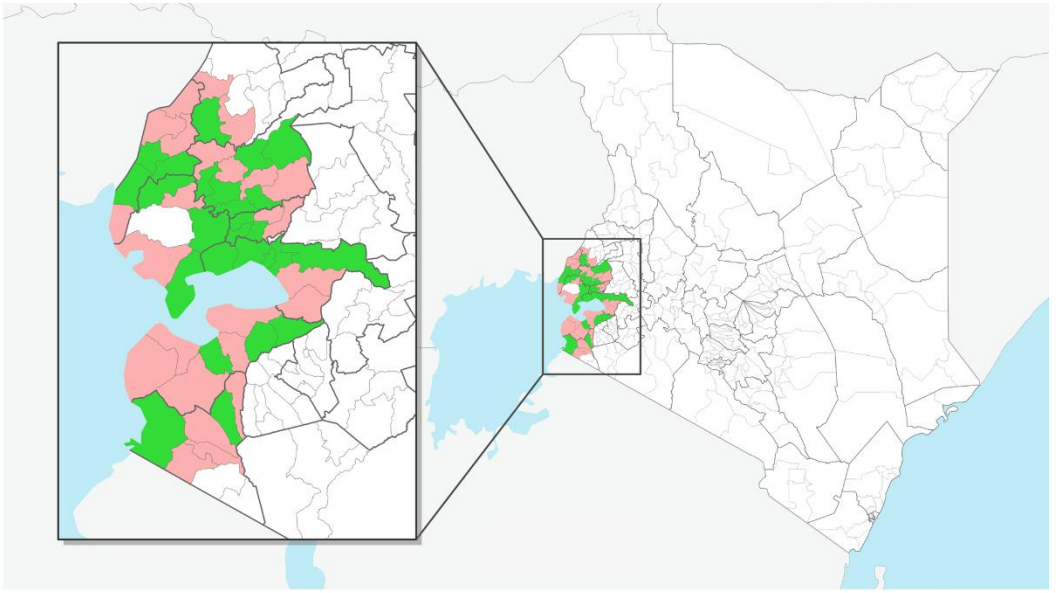
Expanded: 20 Feb 2023



Kenya

First introduced: 13 Sept 2019

Expanded: 7 March 2023



MVIP vaccinating district **(vaccine introduction through EPI; sentinel hospital surveillance; community-based mortality surveillance)**

MVIP comparator district (**initially non-vaccinating – now introducing using donated vaccine doses available through end of MVIP**)

Non MVIP district

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

→ These data, alongside earlier clinical evidence, informed the WHO recommendation

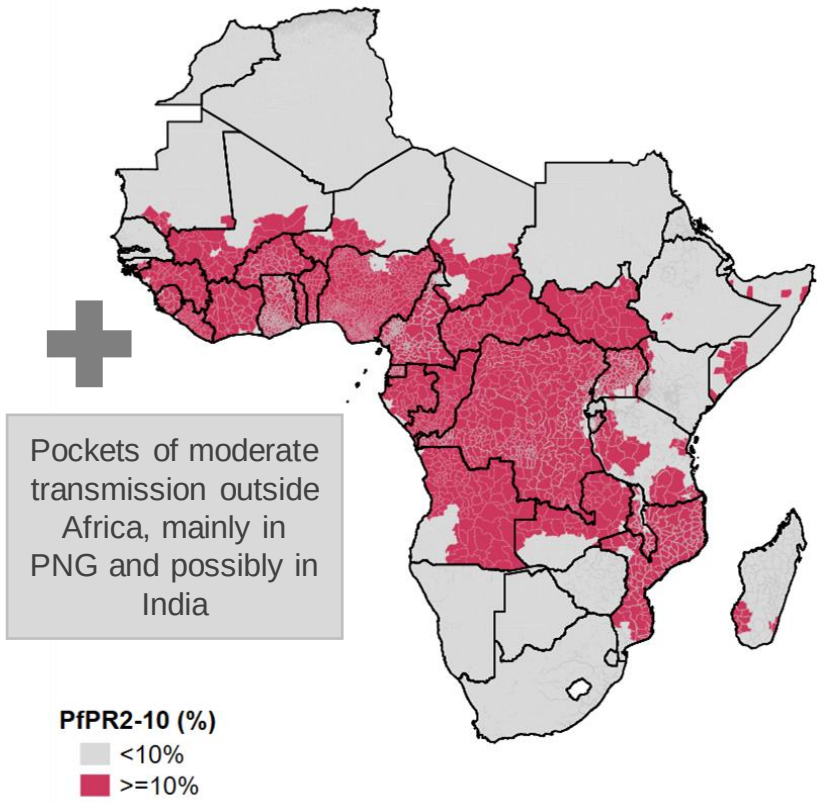
1. **Feasibility:** Vaccine delivery is feasible, with good uptake and coverage through the routine systems, no impact on uptake of other vaccines, insecticide-treated bed nets (ITNs), care-seeking behavior

2. **Safety:** Vaccine is safe; no new safety signals identified (now after over 4 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. During 24 months after vaccine introduction:
   - 32% (95% CI 8, 46%) reduction in hospitalized severe malaria
   - Reduction in all-cause mortality

4. **Equity:** High coverage means the vaccine reaches children who are not using other forms of prevention, increasing access to malaria prevention interventions to > 90%

WHO recommendation: Oct 6, 2021



P. falciparum parasite prevalence ($PfPR_{2-10}$) estimates, 2019. Source: MAP 2019

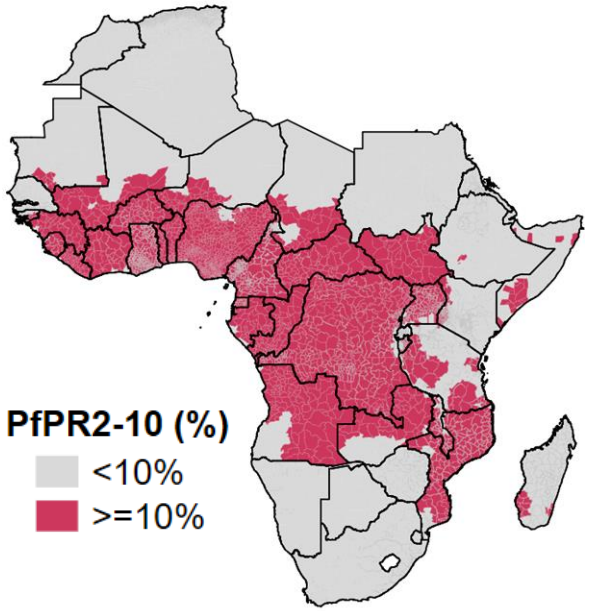
WHO recommends the RTS,S/AS01 malaria vaccine be used for the prevention of *P. falciparum* malaria in children living in regions with moderate to high transmission as defined by WHO

The challenge of meeting high demand with limited supply

Credit: WHO/Fanjan Combrink.

Challenge: Initial vaccine supply insufficient to meet demand

Over **25 million children** are born each year in regions with moderate to high malaria transmission



Pockets of moderate transmission outside Africa, mainly in PNG and possibly in India

P. falciparum parasite prevalence ($PfPR_{2-10}$) estimates, 2019.
Source: MAP 2019

>80-100 million doses per year
likely needed

Demand

18 million doses over 2023 - 2025

Supply

One manufacturer, recent scale-up to manufacture commercial doses, Retiring facility - tech transfer required

Gavi confirms unprecedent demand from countries to introduce the malaria vaccine

Since Gavi opened applications in July 2022:

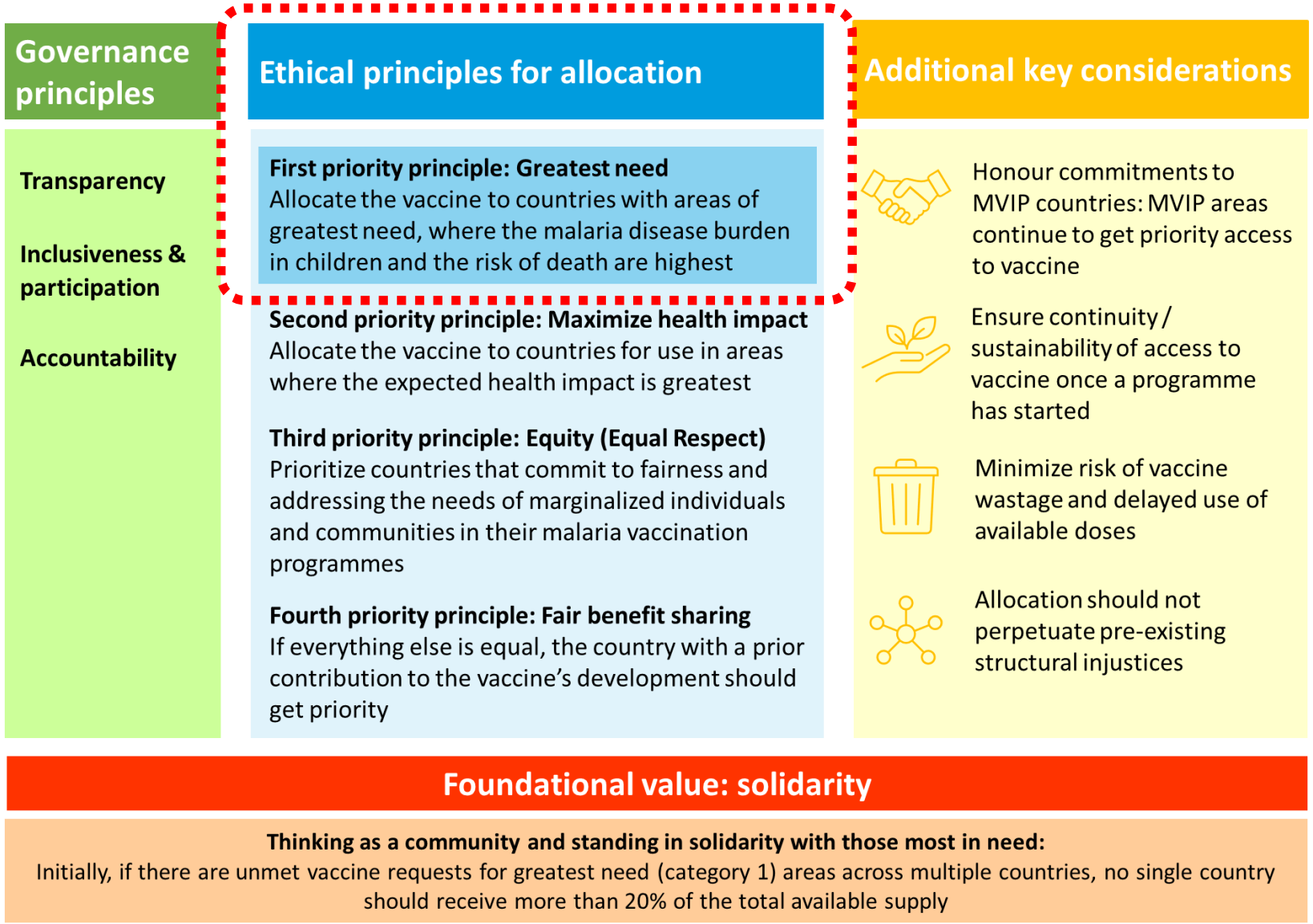
28+ Countries expressed interest in applying for Gavi support to introduce

20 Countries submitted an application

14 Countries approved to receive support → Planning for introduction in Q1-Q2 2024

4 Applications currently under review

WHO supported development of Framework for the allocation of limited malaria vaccine supply

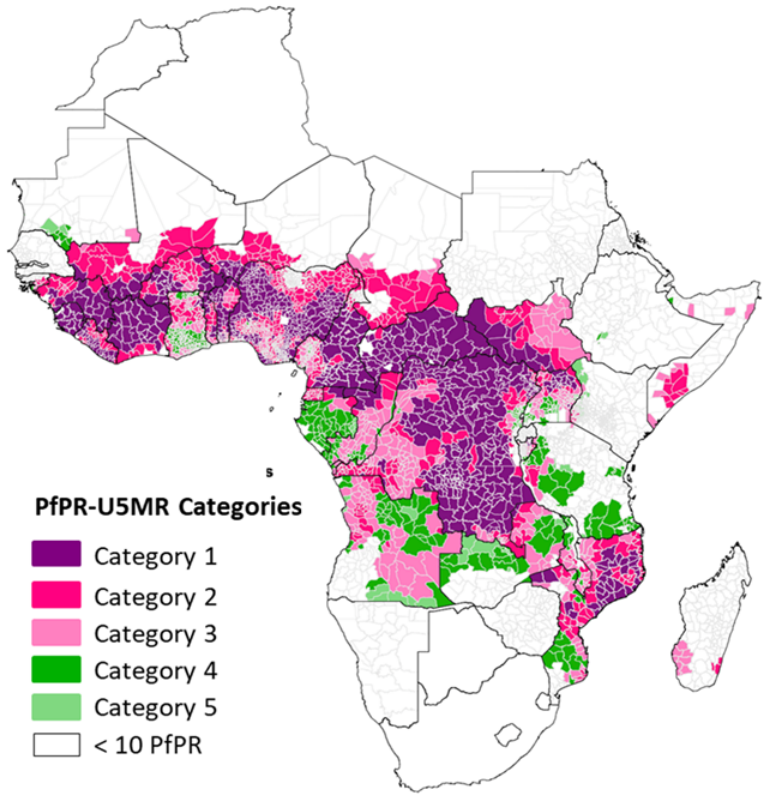


Source: Framework for allocation of limited malaria vaccine supply. WHO 2022. Available on WHO website

Illustration of “need” classification

Composite classification of malaria prevalence and all-cause under-five mortality as proxy for “need”

Category	Possible combinations		
	Malaria prevalence		All-cause under-five mortality
1 Greatest need	PfPR 20-<40%	&	U5MR >=9.5%
	PfPR >=40%	&	U5MR >=9.5%
	PfPR >=40%	&	U5MR 7.5-<9.5%
2	PfPR 10-<20%	&	U5MR >=9.5%
	PfPR 20-<40%	&	U5MR 7.5-<9.5%
	PfPR >=40%	&	U5MR 6-<7.5%
3	PfPR 10-<20%	&	U5MR 7.5-<9.5%
	PfPR 20-<40%	&	U5MR 6-<7.5%
	PfPR >=40%	&	U5MR <6%
4	PfPR 10-<20%	&	U5MR 6-<7.5%
	PfPR 20-<40%	&	U5MR <6%
5	PfPR 10-<20%	&	U5MR <6%

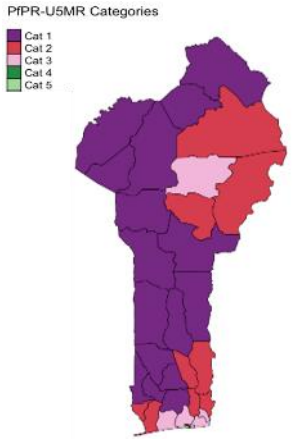


Map is illustrative based on global estimates (PfPR from 2019 Malaria Atlas Project; mortality from 2015 IHME). Countries will identify areas of highest burden and need within its own borders based on best available local evidence and the broader context of sub-national tailoring of malaria interventions

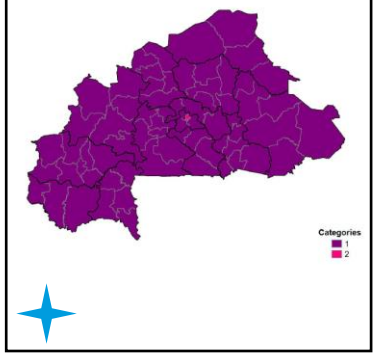
Country-specific stratification of areas by category of need

Developed by countries that applied for Gavi support in January 2023

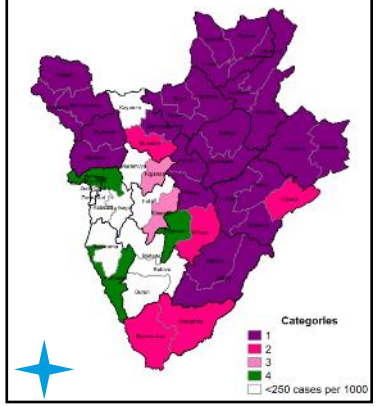
Benin



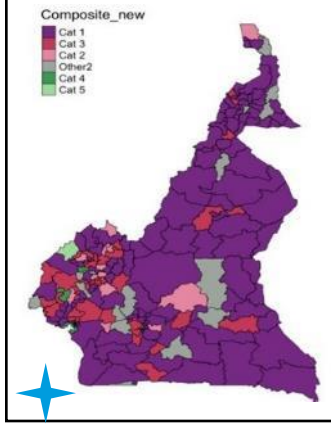
Burkina Faso



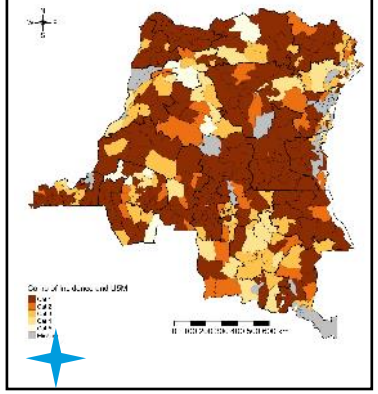
Burundi



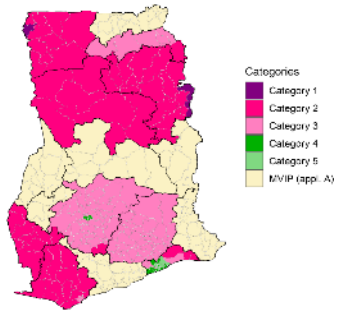
Cameroon



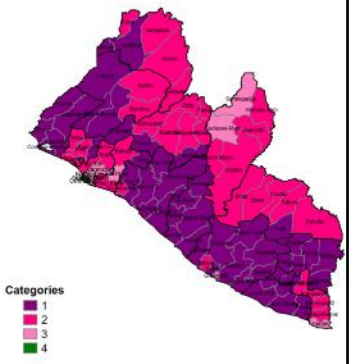
DR Congo



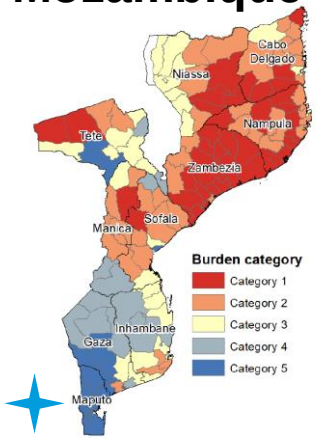
Ghana



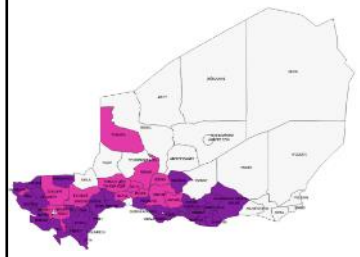
Liberia



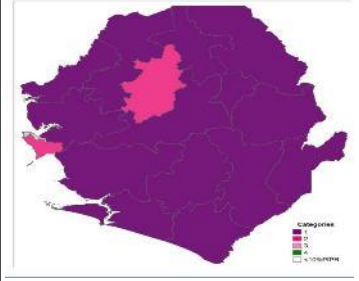
Mozambique



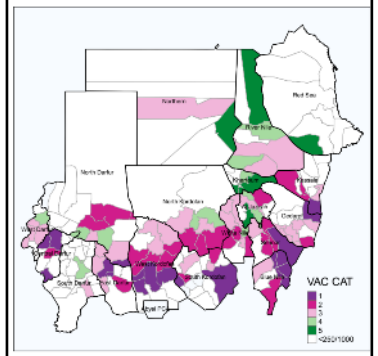
Niger



Sierra Leone



Sudan



Uganda

= country affected by solidarity cap (max. 1 million vaccine doses / year ; requiring further prioritization within category 1 areas)

The challenge in bringing a vaccine targeted to LMIC through development to delivery

Pilot recommendation and lack of high-income market: negative effect on supply of first malaria vaccine

- Pilot recommendation (vs. recommendation for widespread use) resulted in no demand during the pilot period
  - If there was a vaccine market in HIC, manufacturing would have continued to scale, during the period before a WHO recommendation and prequalification (PQ)
  - Sufficient vaccine could have been available at the time of a WHO recommendation
- Manufacturer could not assume demand would materialize; demand dependent on:
  - WHO recommendation, prequalification, funding mechanism established, co-financing reasonable, valued
  - Continuing manufacturing with the assumption that demand will materialize - costly and risky
- Second vaccine that comes to market will have clear visibility into high demand
  - Risk lower for committing resources, may result in more rapid scale up
- Importance of a healthy market (2+ vaccine manufacturer)
  - Vaccine security, cost reduction

Summary

1. The complexity of the malaria parasite, immune evasion strategies, lack of a correlate of protection complicate development of malaria vaccines
2. The Malaria Vaccine Pilot Implementations have shown that the RTS,S/AS01 vaccine is safe, feasible to deliver, and has important impact even in the setting of good coverage with other malaria control tools
3. In the setting of high demand and limited available supply, a Framework for allocation is guiding equitable access of the vaccine to children where need is highest, with phased introduction to other areas as supply availability increases
4. Although a vaccine may be found to be a highly effective intervention, the lack of a dual market can pose considerable challenges and risks to successful clinical development and large-scale deployment; delayed deployment may further complicate supply availability
5. Accelerating increased malaria vaccine supply is critical and a priority for WHO and partners – if a second pre-erythrocytic vaccine, R21/MatrixM, is recommended for use, it could help reduce the gap between demand and supply

- pr

MVIP is a collaboration across many partners

World Health Organization

PATH

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

gsk

unicef

Ministry of Health
Ghana, Kenya Malawi

REPUBLIC OF KENYA

MINISTRY OF HEALTH

MINISTRY OF HEALTH
REPUBLIC OF GHANA

Evaluation partners
Commissioned by WHO

Ghana

UNIVERSITY OF GHANA
SCHOOL OF PUBLIC HEALTH

UNIVERSITY OF HEALTH AND ALLIED SCIENCES
Health for Development

NOGUCHI MEMORIAL INSTITUTE FOR MEDICAL RESEARCH
UNIVERSITY OF GHANA , LEGON

Kenya

CDC

KEMRI | Wellcome Trust

CDC Foundation
Together our impact is greater

Malawi

UNIVERSITY OF MALAWI
COLLEGE OF MEDICINE

UNC PROJECT
Lilongwe, Malawi

WHO Malaria Vaccine Team
IVB/GMP/AFRO
-Eliane Furrer
-John Francis
-Kristen Kelleher
-Rafiq Okine
-Cindy Bergstrom
-Lindsey Wu
-Mayuko Takamiya
-Nelli Westercamp, CDC

Funders

Gavi The Vaccine Alliance

The Global Fund

Unitaid

External monitor

Pharmalys Clinical Research

ClinWin Research Services
Quality. Efficiency. Ethics

Reference laboratories

MRC Unit The Gambia

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Partners qualitative study Commissioned by PATH

UNIVERSITY OF HEALTH AND ALLIED SCIENCES
Health for Development

Malawi-Liverpool-Wellcome Clinical Research Programme

CDC

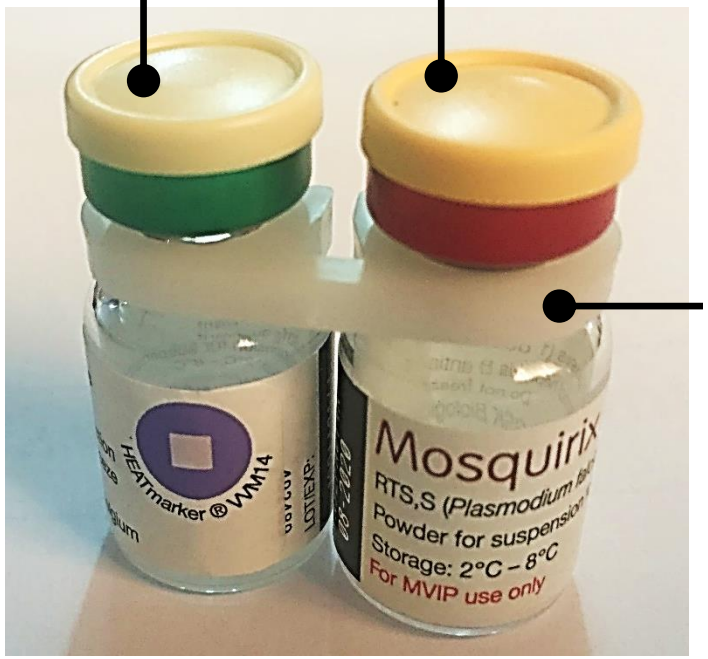
LSTM

Thank you!

RTS,S/AS01 product characteristics

Adjuvant AS01
liquid
(green ring)

Antigen RTS,S
lyophilized
(red ring)

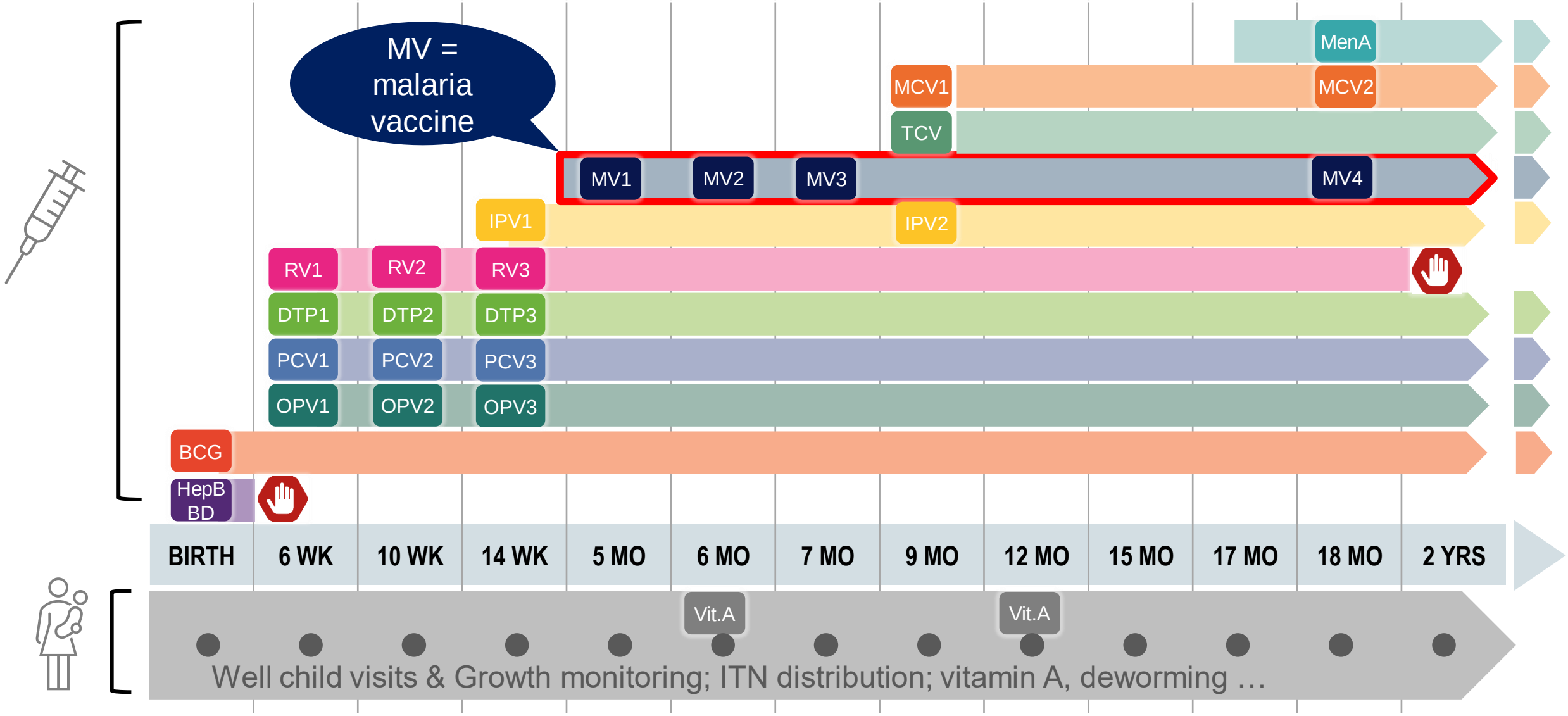


Vials are clipped together to reduce the chance of reconstitution error

- 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.
- Storage 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

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



Source: Adapted from the WHO 2YL guide (Annex 4); HepB