OPT-MVAC
Optimising malaria vaccine uptake

Project funded by

OPT-MVAC, the European Vaccine Initiative & Medicines for Malaria Venture welcome you to

OPT-MVAC webinar: Lessons from the MVPE-CC project

- **Session 1: Overview of the MVPE-CC project results and key lessons, including implementation experiences and contextual challenges.**
- **Session 2: Reflections on how MVPE-CC insights guide programme planning, translate into practical programme actions, and adapt to contextual factors.**
- **Session 3: Panel discussion on how MVPE-CC learnings can support OPT-MVAC objectives, from technical operations to programme planning and future field implementation.**

Session 1

Results and lessons learned from the MVPE-CC project

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OPT-MVAC webinar on MVPE-CC project

The Malaria Vaccine Pilot Evaluation-Case Control Study (MVPE-CC)

Prof Kwaku Poku Asante and Dr Thomas Gyan on behalf of the MVPE-CC Consortium

20 March 2026

Background

Credit: WHO/F.Combrink

Vaccine efficacy (VE) with 3 or 4 doses RTS,S/AS01, by follow-up time 5-17 month (M) age group; Phase 3 clinical trial 2009 - 2014

Clinical Malaria*	RTS,S/AS01 VE (95% CI)
12M f-up	51% (48,55)
18M f-up	46% (42,50)
~48M f-up** 3-dose	26% (21,31)
~48M f-up** 4-dose	39% (34,43)

Severe Malaria	RTS,S/AS01 VE (95% CI)
12M f-up	45% (24,60)
18M f-up	38% (18,53)
~48M f-up** 3-dose	-2% (-31,20)
~48M f-up** 4-dose	32% (9,48)

*Clinical malaria includes uncomplicated and severe malaria
SE = Study end, **median 48 months follow-up
Source: Lancet, 2015. RTS,S Trials Partnership

- VE wanes over time
  - Dose-4 increases vaccine efficacy and prolongs protection against clinical and severe malaria
- In 3-dose group, VE against severe malaria lost, potentially due to rebound
  - A 4th dose prevents this rebound

RTS,S/AS01 Malaria Vaccine Implementation Programme (MVIP): impact on severe malaria and all-cause mortality among children age-eligible for vaccination

- During the first 4 years of RTS,S implementation in the pilot countries, there was a substantial impact on all-cause mortality and on the incidence of hospital admission with severe malaria in eligible age groups of children:
  - **13% (95%CI 2%-22%) reduction in all cause deaths excluding deaths due to injury,**
  - 22% (95%CI 6%-37%) reduction in incidence of hospital admission with severe malaria
- This impact was achieved in the context of relatively high coverage of the three primary doses (75%) and despite suboptimal uptake of dose 4 (40%).

- Safety data further strengthens the evidence on safety reviewed by WHO in 2021.

Malaria Vaccine Pilot Implementation case-control study – MVPE-CC

This project is part of the EDCTP2 programme supported by the European Union (RIA2020S-3310-MVPE-CC)

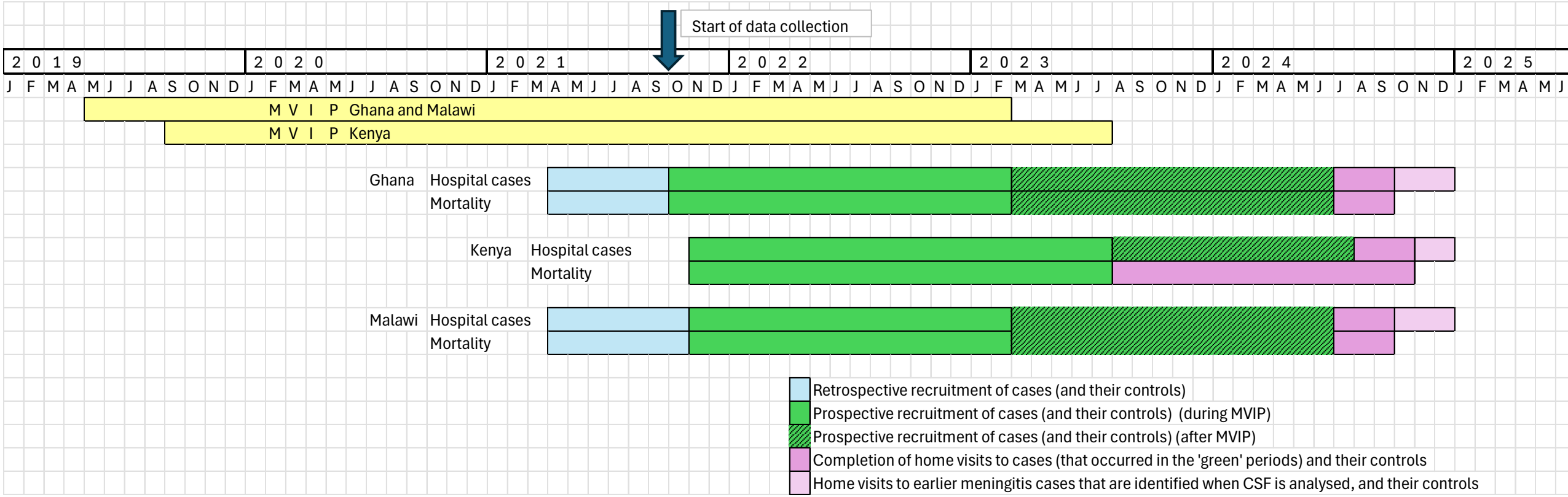
This project leveraged the WHO led Malaria Vaccine Pilot Evaluation

Objectives

- With respect to severe malaria, aimed to estimate:
  - effectiveness of three doses
  - effectiveness of four doses and incremental effectiveness of the fourth dose
  - magnitude of any rebound effect or waning of protection from primary dose series, in children with three doses but not four

- With respect to safety outcomes, aimed to assess association of RTSS with meningitis; with cerebral malaria; and determine if the effect of RTS,S on mortality differs by gender

Time periods for recruitment of cases and controls



Cases were eligible to be recruited if they occurred in these periods:

	Hospital	Mortality
Ghana:	1 Apr 2021 – 30 Jun 2024	1 Apr 2021 – 30 Jun 2024
Kenya:	1 Nov 2021 – 31 Jul 2024	1 Nov 2021 – 12 Jul 2023
Malawi:	14 Apr 2021 – 30 Jun 2024	14 Apr 2021 – 30 Jun 2024

Age ranges for vaccine-eligible cases:

Start of study	End of study
6-30months	6-59months
6-37months	6-59months
5-29months	5-59months

Study design: Cases and controls

Cases **(using same case definitions from MVPE):**

severe malaria (including cerebral malaria)
probable or confirmed meningitis
deaths (any cause excluding injury)

Controls

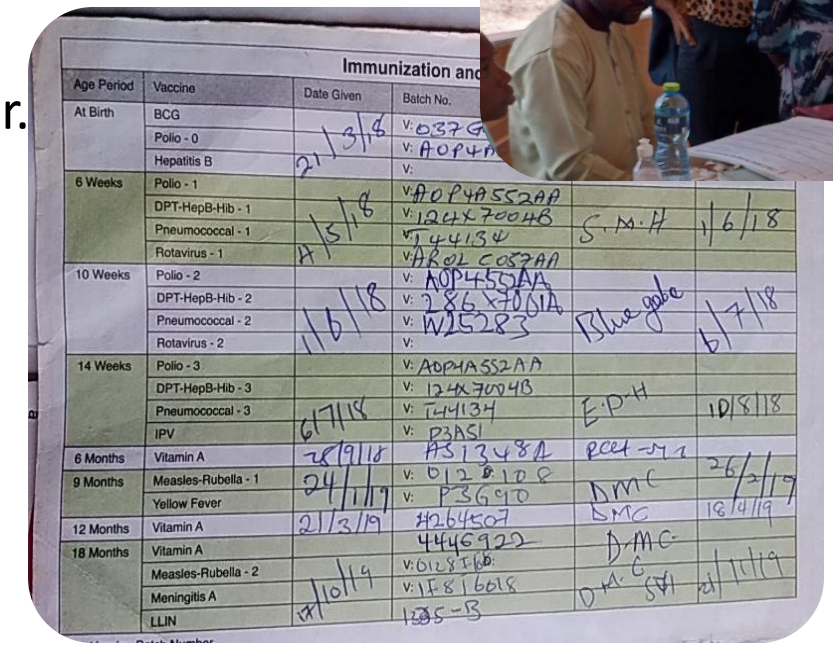
For each type of case, **four control children born within 1 month** of the date of birth of the case were recruited from the neighbourhood of the case's home, after moving a distance of at least 100m from the home of the case.

Cases were visited at home to confirm details recorded in the hospital and collect further information about the case child and their household. The **same field team then recruited controls** from the same neighborhood.

Study design: vaccine documentation

For cases and controls, **vaccination status** was determined:

- From home-based record (HBR)
- from the clinic registers
- Photos taken to permit verification later.



Age Period	Vaccine	Date Given	Batch No.
At Birth	BCG		
	Polio - 0	21/3/18	
	Hepatitis B		
6 Weeks	Polio - 1		
	DPT-HepB-Hib - 1	4/5/18	
	Pneumococcal - 1		
	Rotavirus - 1		
10 Weeks	Polio - 2		
	DPT-HepB-Hib - 2	1/6/18	
	Pneumococcal - 2		
	Rotavirus - 2		
14 Weeks	Polio - 3		
	DPT-HepB-Hib - 3	6/7/18	
	Pneumococcal - 3		
	IPV		
6 Months	Vitamin A	25/9/18	
9 Months	Measles-Rubella - 1	24/1/19	
	Yellow Fever		
12 Months	Vitamin A	21/3/19	
18 Months	Vitamin A		
	Measles-Rubella - 2	4/10/19	
	Meningitis A		
	LLIN		

Target sample size for each outcome measure

Outcome	Total cases recruited that have vaccine documentation (excluding replacement cards)	Target sample size	Effect size	Assumed coverage
Meningitis	49	46	5-fold excess, received any RTS,S/AS01	80% dose 1
Cerebral malaria	147	180	2-fold excess, received any RTS,S/AS01	80% dose 1
Deaths	860	700	Interaction, received any RTS,S/AS01, (2-fold excess in girls compared to boys)	80% dose 1
Severe malaria	1,277			
Eligible for 3 doses, but not for dose 4	504	330	30% reduction in those with 3 doses compared to 0 doses	70% dose 3
Eligible for dose 4	689	700	50% excess compared to 0 doses (rebound effect)	40% dose 4

Effectiveness of RTS,S/AS01 doses 1,2,3 against severe malaria up to the age when the 4th dose could be given
(22 months of age in Malawi, 24 months in Kenya, and in Ghana 24 months until 20 Feb 2023 when the age was changed to 18 months)

The period from 0.5 months after the dose, until the age scheduled for dose 4:	
Number of doses:	**% effectiveness (95% confidence interval)**
0	
1	**-24% (-76%, 12%)**
2	**21% (-14%, 45%)**
3	**56% (40%, 67%)**

56% effectiveness against severe malaria, from receipt of dose 3, until eligible for dose 4 (**about 15 months**)

No evidence that 1 or 2 doses protective, 3 doses are needed

Among children eligible for dose 4, effectiveness of RTS,S/AS01 doses 1,2,3,4 against severe malaria

Number of doses	% effectiveness (95% confidence interval)
0	
1	5% (-49%, 39%)
2	-26% (-90%, 16%)
3	35% (15%, 50%)
4	54% (39%, 66%)

From the age when children were eligible for dose 4 (22 months in Malawi, 24 months in Kenya, 24 months in Ghana):

- Children who had only 3 doses: 35% protection against severe malaria*
- 1 or 2 doses only: no evidence of protection

From receipt of dose 4: children who had 4 doses: 54% protection*

- **Continued benefit of 3 doses**
- **Significant added benefit of the 4th dose**

* Average effectiveness over a period of about 24 months

Effectiveness of RTS,S against cerebral malaria

- **Vaccination with RTSS was associated with reduced incidence of cerebral malaria.**
  - **Vaccine Efficacy (VE) of 3 doses 53%**
  - **VE of 4 doses 74%**

- **(But: no statistical evidence that this protection against cerebral malaria differed from that for other forms of severe malaria)**

Key findings on safety

Meningitis

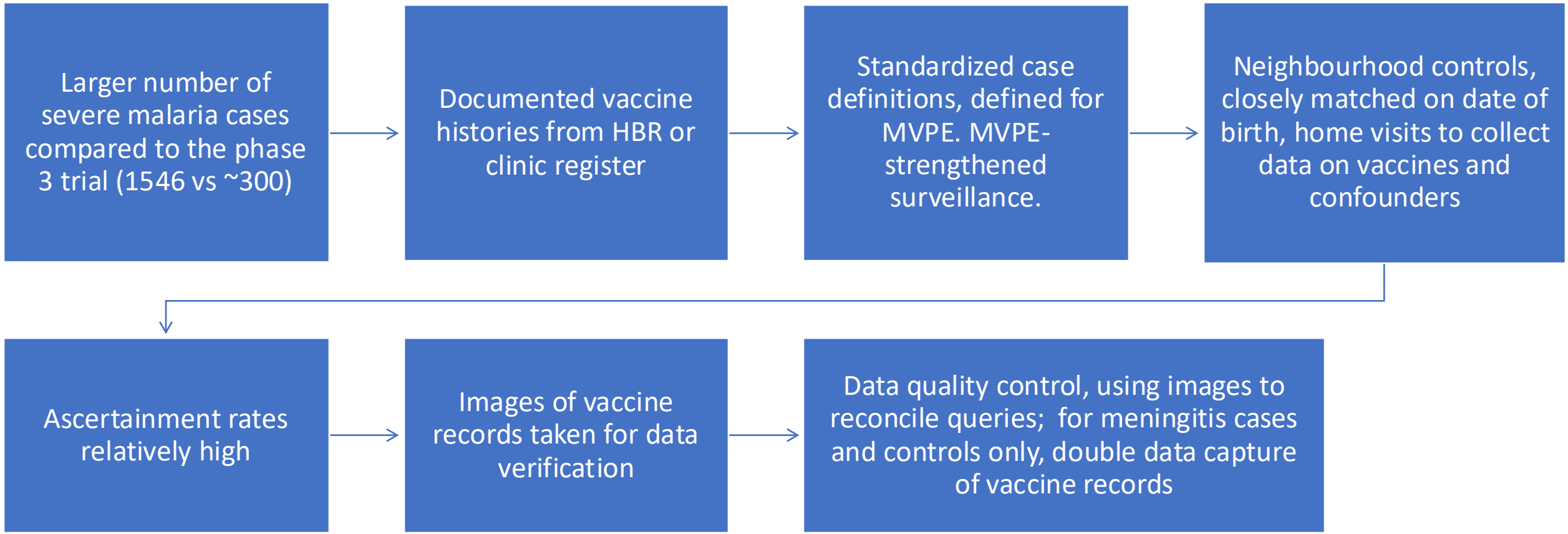
Recruited		Documented vaccine history (replacement HBR excluded)		Received 1 or more doses of RTSS	
Cases	Control	Cases	Control	Cases	Control
57	226	49 (86.0%)	179 (79.2%)	38/49 (77.6%)	134/179 (74.9%)

- There was **NO evidence** that **Meningitis** was **associated with RTSS vaccination** **adjusted odds ratio 0.96 (95%CI 0.38,2.4).**

Mortality

- There was **NO evidence** that **the effect of RTSS on mortality differed between girls and boys**

Strengths


Larger number of severe malaria cases compared to the phase 3 trial (1546 vs ~300)
Documented vaccine histories from HBR or clinic register
Standardized case definitions, defined for MVPE. MVPE-strengthened surveillance.
Neighbourhood controls, closely matched on date of birth, home visits to collect data on vaccines and confounders
Ascertainment rates relatively high
Images of vaccine records taken for data verification
Data quality control, using images to reconcile queries; for meningitis cases and controls only, double data capture of vaccine records

Limitations

1. Some cases were recruited retrospectively - ITN use and other confounders may have changed
2. When replacement vaccine records are issued, earlier doses not always recorded
3. Children with 3 doses might have undocumented 4^{th} doses (especially in clinic registers), a potential bias
4. Residual confounding: although we adjusted for covariates it is likely residual confounding remains

RTS,S/AS01 MVIP DSMB assessment of safety – Case-control study

Key conclusions on safety outcomes

- Meningitis: The case-control study showed **no increased risk of meningitis in children who received the RTS,S/AS01 malaria vaccine** compared with unvaccinated children.

- Cerebral malaria: The results showed **no evidence of increased risk of cerebral malaria**; the analysis indicates a **protective effect of RTS,S/AS01 against cerebral malaria**.

- Severe malaria rebound: **The data did not show evidence of severe malaria 'rebound' in children who received 3 doses**. The analysis shows protection from 3 doses of RTS,S/AS01. The protection of RTS,S/AS01, farther out from receipt of dose 3 may decrease relative to natural immunity (controls), but at no time point presented was there an increased risk of severe malaria among vaccinated children relative to controls.
- Imbalance in sex-specific mortality: **There was no evidence of an increased risk in mortality in girls who received the RTS,S vaccine.**

World Health Organization

*MVIP DSMB meetings held: February 2023, June 2023, October 2023, November 2024, and May 2025

Strategic Advisory Group of Experts (SAGE) and the WHO Malaria Policy Advisory Group (MPAG) recommendations

Policy impact

After a review of all available evidence, showing that the **four-dose malaria vaccine schedule provides greater protection against clinical and severe malaria** than a three-dose schedule in moderate to high transmission settings

SAGE and the WHO Malaria Policy Advisory Group (MPAG) **reaffirmed its recommendation for the use of the four doses as the recommended schedule**.

The case-control study embedded in the Malaria Vaccine Implementation Programme (MVIP), including children aged < 5 years, shows that a **4-dose schedule reduces severe malaria cases by around 54%** through the study period, and **the fourth dose provides a 30% incremental effectiveness above 3 doses** in reducing severe malaria.

There was **no evidence of rebound** among children who missed the fourth dose.

The full SAGE/MPAG report was published in the Weekly Epidemiological Record on 5 December 2025.

Acknowledgments

RTS,S/AS01 Malaria Vaccine Pilot Evaluations Case-control study consortium (MVPE-CC)

GHANA HEALTH SERVICE
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European Vaccine Initiative

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Financial support

E D C T P

This project is part of the EDCTP2 Programme supported by the European Union

With additional financial contributions to maintain the hospital and mortality surveillance beyond the completion of the MVPE

Gavi
The Vaccine Alliance

Session 2

Reflections and implications from the MVPE-CC project

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Implications of the findings from the severe malaria case control study

Paul Milligan

London School of Hygiene&Tropical Medicine

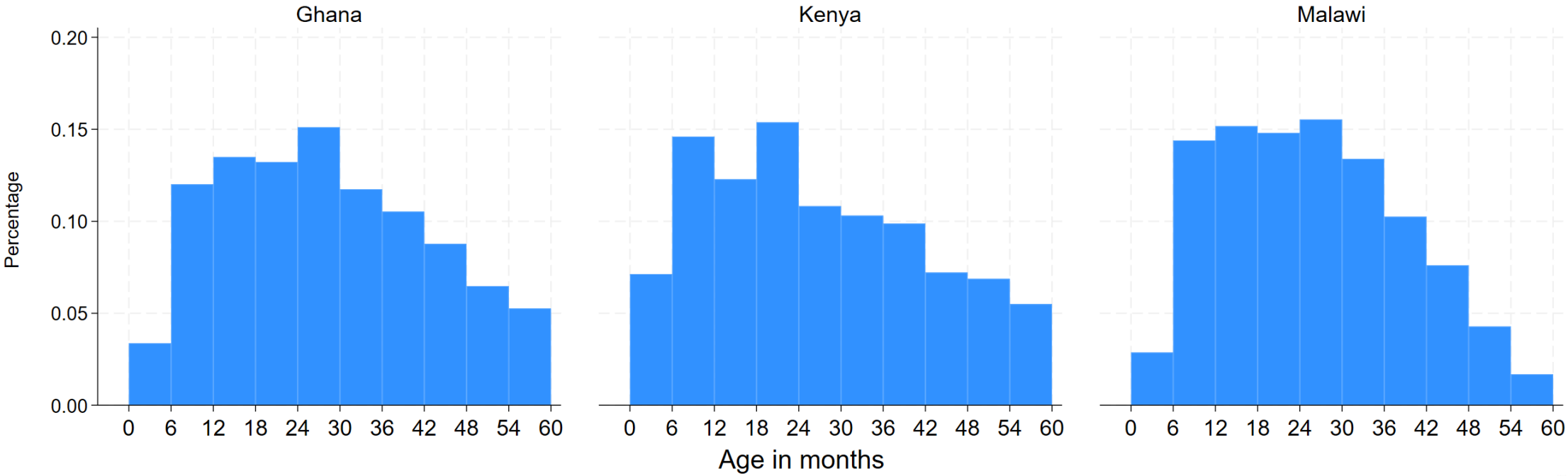
EDCTP

Implications

- No evidence of a rebound effect in severe malaria
  - Protection from 3 doses continues, so children who miss dose 4 have some protection against severe malaria remaining from dose 3
  - Concerns about being able to achieve high coverage of dose 4 should not hold back implementation or scale-up
- Dose 4 provides significant additional protection against severe malaria (including against cerebral malaria)
  - Re-allocating 4th dose to vaccinate more children with 3 doses is **not** recommended
  - Efforts should be made to improve vaccine uptake in the second year of life
- Further evidence in relation to safety
  - Not only were there no excess cases of meningitis or cerebral malaria or deaths in girls in districts where the vaccine was introduced, we now have evidence at the individual level that there is no increased risk of these events in children who are vaccinated

Malaria vaccine targets ages when children are most vulnerable
High burden in the age range targetted by dose 4

Age distribution of severe malaria admissions MVIP comparison areas 2019-2023



Graphs by c

Levels & Trends in Child Mortality | Report 2025
Estimates developed by the United Nations Interagency Group for Child Mortality Estimation

Mortality:
Malaria the leading cause of post-neonatal under-5 mortality (UNICEF 2026)

IGME | unicef | World Health Organization | WORLD BANK GROUP | United Nations

Ghana experience: steps to improve uptake of the 4th dose

Ghana's experience: Schedule change of the fourth dose of Malaria Vaccine to reduce drop-out

Amponsa-Achiano, K., Tanko, M. N., Tweneboah, P., Osei-Sarpong, F., Okine, R., Bawah J. T

Background

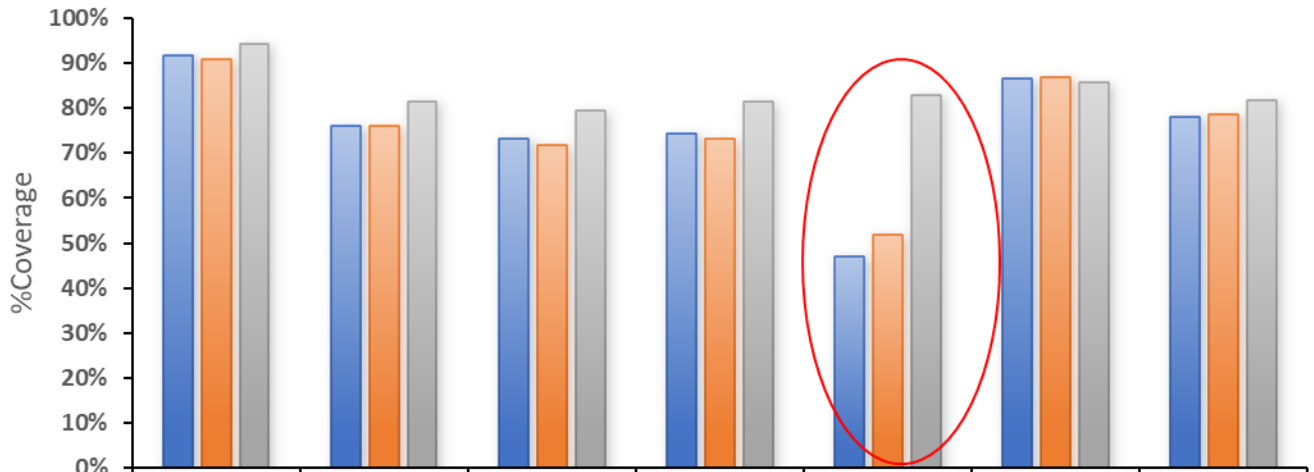
Ghana introduced the RTS,S malaria vaccine into its national immunization program in 2019 through the Malaria Vaccine Implementation Program (MVIP). The MVIP was designed by the World Health Organization (WHO) to assess the feasibility of delivering four doses of the vaccine, safety, and impact of the RTS,S vaccine in real-world settings. The initial dosing schedule for the RTS,S vaccine was 6, 7, 9, and 24 months of age. This schedule was chosen to align with existing immunization schedules and to ensure that children received the full course of the vaccine.

4th dose administration began in October 2020, but by December 2021, only 47% of eligible children had received it, despite intensive efforts to strengthen defaulter tracing

In early 2022, the country reviewed strategies to include more frequent Periodic Intensification of Routine Immunization (PIRI) activities to improve fourth-dose coverage. This resulted in a marginal increase from 47% in 2021 to 52% in 2022

In November 2022, NITAG-Ghana reviewed the evidence and recommended changing the fourth dose schedule to 18 months of age. This leveraged Ghana's strong second year of life (2YL) platform and aligned the visit with MR2, Men A, ITN provision, Vitamin A supplementation, and growth monitoring. This led to a rapid increase in coverage from 52% in 2022 to 83% in 2023.

Figure 1: Vaccine coverage in Phase1 districts 2021-2023



	Penta3	MV1	MV2	MV3	MV4	MR1	MR2
2021	92%	76%	73%	74%	47%	86%	78%
2022	91%	76%	72%	73%	52%	87%	79%
2023	94%	81%	80%	81%	83%	86%	82%

Countries planning the introduction of a malaria vaccine should consider a careful review of existing interventions, particularly in the second year of life, that can be leveraged to optimize the uptake of the fourth malaria vaccine dose (and other doses). Effectively planned and well-timed PIRI activities are also critical for sustained improvement in vaccine coverage.

Case control studies

- Useful to monitor efficacy (effectiveness), *which may not be the same everywhere*
  - for communication about the level and duration of protection
  - to understand impact, when combined with coverage surveys
  - to inform optimal timing of 4th dose (and need for 5th?)
- Can be cost efficient but require careful planning and conduct
- Potential for bias, need to ensure:
  - accurate case definition
  - good case ascertainment
  - selection of appropriate controls
  - vaccination dates from documented sources
  - consider important confounders
- Outpatient studies are much simpler than severe malaria studies
  - can be undertaken in small number of clinics, in a limited area, over a shorter time
  - may use test-negative controls
  - can choose smaller clinics with well-kept records
  - should employ LDH-based tests to detect malaria

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World Health Organization

Thank you

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Share your perspective - Partagez votre point de vue - Partilhe a sua perspetiva

English

OPT-MVAC aims to optimize malaria vaccine delivery. **Your input will help define priorities for an adapted training programme. A brief survey will identify key needs to strengthen research and knowledge exchange.**

Français

OPT-MVAC vise à optimiser l'administration du vaccin contre le paludisme. **Votre avis aidera à définir les priorités pour une formation adaptée. Une brève enquête précisera les besoins clés pour renforcer recherche et échanges.**

Português

OPT-MVAC visa otimizar a administração da vacina contra a malária. A sua opinião ajudará a definir prioridades para uma formação adequada. **Uma breve pesquisa identificará as necessidades essenciais para reforçar a investigação e a troca de conhecimentos.**

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Session 3

Panel discussion on how MVPE-CC key learnings can support OPT-MVAC objectives

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Thank you!
Merci !
Obrigado!