

Strengthening the evidence for policy on the RTS,S/AS01 malaria vaccine: assessment of safety and effectiveness using case-control studies embedded in the Malaria Vaccine Pilot Evaluation (MVPE-CC)

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On behalf of MVPE-CC

OPT-SMC Workshop

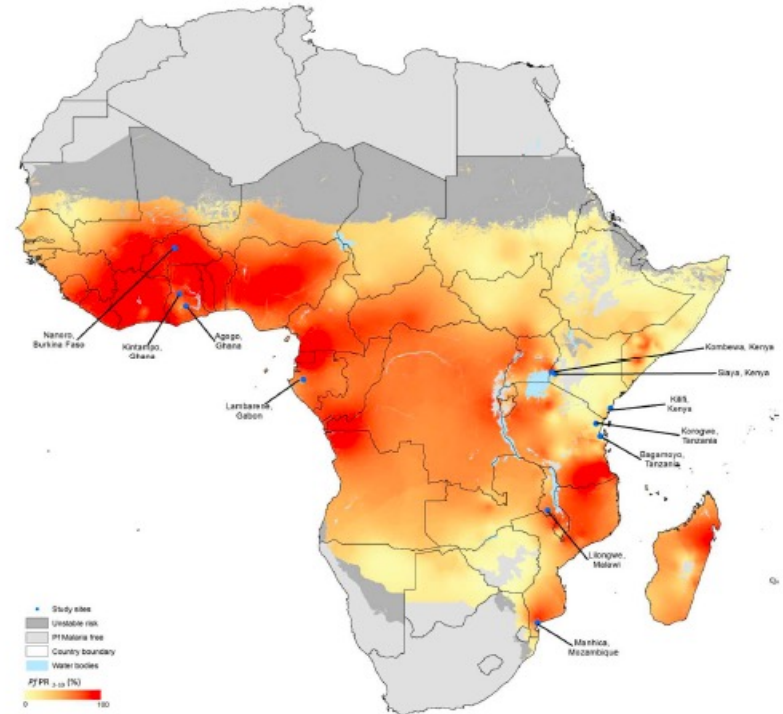
23 -25 January 2023.



Background – First WHO approved Malaria vaccine

- RTSS Malaria vaccine developed over 30 years !!
- Large Phase 2 and 3 trials in Africa between 2006 and 2015
- WHO recommended
 - generating evidence and experience on the feasibility, impact and safety of the RTS,S malaria vaccine in real-life, routine settings in moderate to high transmission settings.

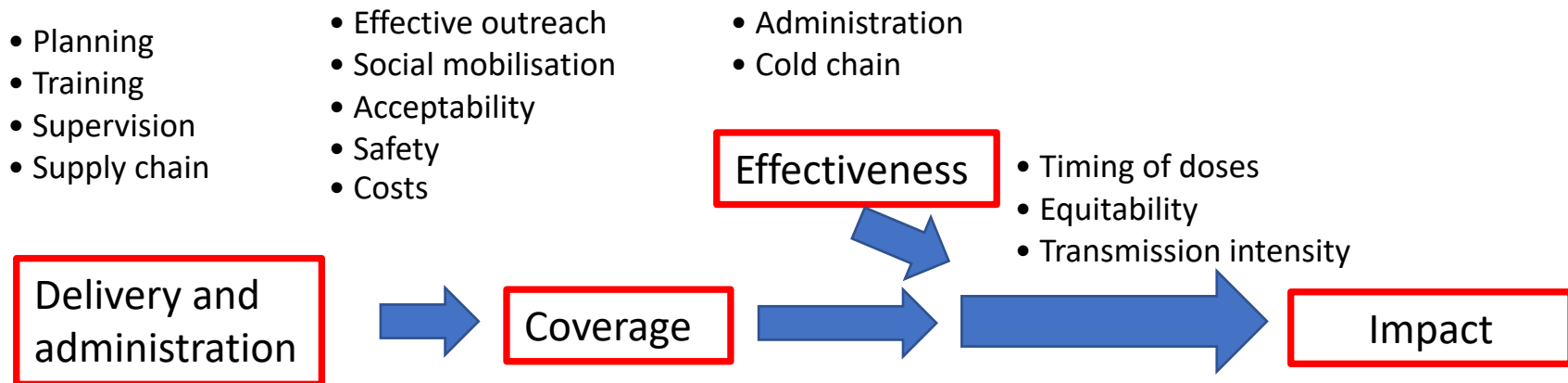
Figure S1. Study sites and malaria endemicity.



Adapted from Hay SI, Guerra CA, Gething, PW et al. A world malaria map: *Plasmodium falciparum* endemicity in 2007. *PLoS Med* 2009; 6(3): e1000048.

Conceptual framework for monitoring and evaluation of malaria vaccine impact

Factors that influence impact:



Methods and measurement considerations:

Administrative records

- Accuracy and completeness of documentation

Household surveys

- Objective participant selection
- Assessment of vaccine status

Pharmacovigilance

- Awareness of health staff and community
- Timely investigation and reporting
- Laboratory support

Case-control studies

- Case definitions
- Selection of controls
- Assessment of vaccine status and dates of doses

Malaria surveillance

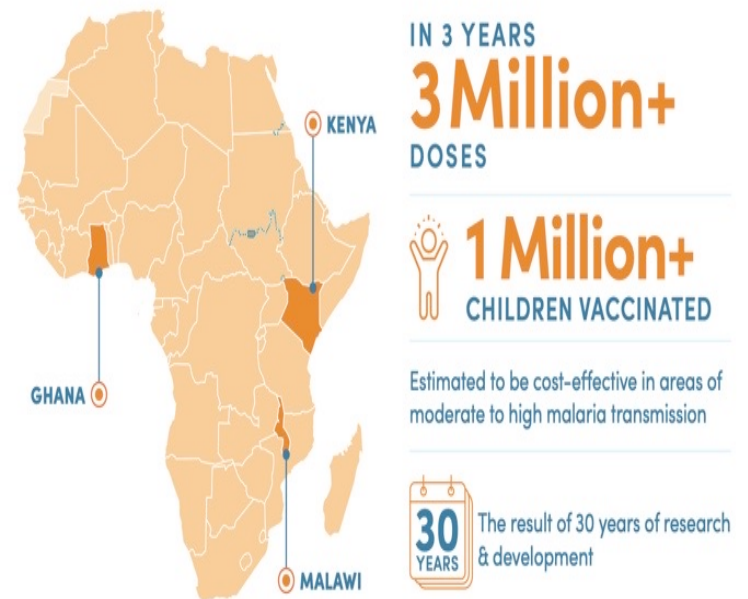
- Parasitological confirmation
- Accuracy, completeness of records
- Relevant age range reported
- Quality of information systems
- Catchment area
- Effects of other interventions
- Changes in policies
- Variations due to climate, locality
- Transmission intensity

Malaria Vaccine Pilot Evaluation

- Started in 2019
- Large evaluation
 - Large surveys to assess feasibility
 - Hospital surveillance to assess safety and impact on hospital admissions and severe malaria
 - Community surveillance to assess impact on mortality
- Impact and safety estimates are at population level and not individual risk
- Large logistic requirements
- Costly to implement under programmatic settings

The RTS,S/AS01 malaria vaccine pilots in Africa

Significantly reduces malaria and life-threatening severe malaria. Since 2019, delivered in childhood vaccination in 3 country-led pilots.



Source: WHO

When is RTS,S likely to be available

- WHO recommended RTS,S malaria vaccine after pilots implementation in Malawi, Ghana and Kenya, 2021
- Gavi to support rollout in eligible countries
- Malawi expanded RTS,S pilot to reach more children 2022
- Rollout in Ghana and Kenya planned for 2023
- Other countries ready to adopt RTS,S
- Evaluation of initial introduction in terms of delivery, uptake especially in second year of life, safety to gather evidence on impact is needed



Source: WHO

Our Innovation

- To use a relatively cheaper case control approach
 - To identify individual safety risk
 - To assess the benefit of 4th dose in real life
 - Assess impact of the vaccination among vaccinated children
 - Severe malaria
 - mortality
 - Other outcomes
- Develop this approach as an evaluation tool for Malaria Elimination Programmes when the malaria vaccine is introduced in their countries
- Can be extended to other vaccines

Role of case-control studies in malaria elimination programmes

- To complement other forms of evaluation by EPI and NMEP
- Approach can be use to:
 - assess efficacy against clinical malaria, severe malaria. The approach could be combine with coverage surveys to measure uptake and surveillance to monitor malaria burden
 - look at duration of protection and the need for additional booster doses
 - Strengthen post vaccine evaluation as the safety questions have been resolved by ongoing evaluation

Introducing the malaria vaccine pilot evaluation-case-control studies

Ghana, Kenya, Malawi



MVPE-CC questions

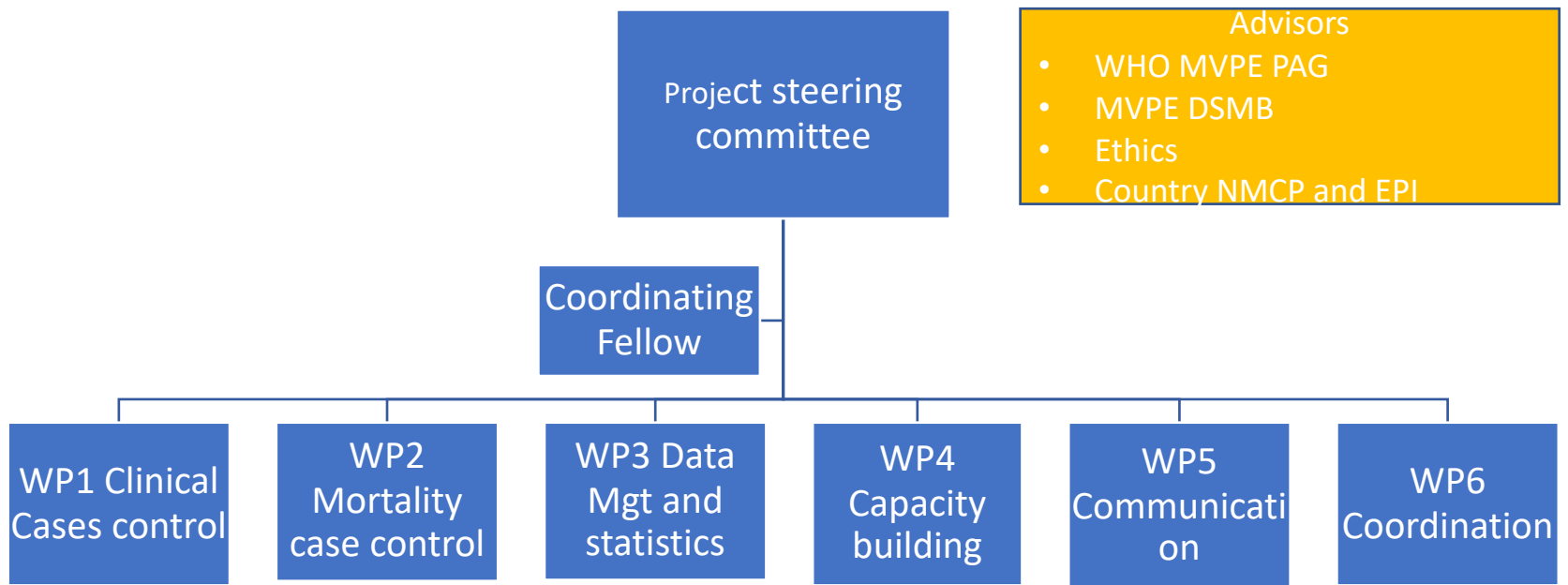
1. Are children who receive RTS,S vaccination at increased risk of meningitis compared to unvaccinated children?
2. Are children who receive RTS,S vaccine at increased risk of cerebral malaria compared to unvaccinated children?
3. Is the incidence of severe malaria increased in children who received 3 doses, but failed to receive a 4th dose, compared to children who did not receive the vaccine? (the rebound effect)
4. What is the effectiveness of RTS,S (following 3 doses, and following the 4th dose) in preventing severe malaria?
5. Is there any evidence that RTS,S vaccine increases mortality in girls, or is less effective in preventing death in girls, compared to boys?

MVPE-CC Consortium members

- Kintampo Health Research Centre (KHRC)
- European Vaccine Initiative (EVI)
- London School of Hygiene and Tropical Medicine (LSHTM)
- African Research Collaboration for Health Limited (ARCH)
- Kenya Medical Research Institute (KEMRI)
- University of Malawi, College of Medicine (CoM)
- PATH - USA

Team	Primary lead institution	Co-lead/involved
Project coordination	KHRC	EVI
Clinical outcomes case-control	ARCH	KHRC, CoM, KEMRI, EVI, LSHTM
Mortality outcome case-control	CoM	KHRC, ARCH, KEMRI, EVI, LSHTM
Methodology	LSHTM	KHRC, ARCH, KEMRI, CoM, EVI
Capacity building	KHRC	ARCH, KEMRI, CoM, EVI, LSHTM
Community engagement	PATH	EVI, ARCH, KEMRI, CoM, LSHTM

MVPE-CC Governance structure



Design of the MVPE-Case-control studies

- Three types of cases:
 - **Meningitis (probable or confirmed)**
 - **Severe malaria** including **Cerebral malaria** diagnosed in MVPE sentinel hospitals surveillance
 - **Death**
- For each case, 4 community controls matched on date of birth and neighbourhood are being recruited concurrently

Case definitions

- **Meningitis:** A case of meningitis will be defined as a child who resides in an RTS,S/AS01 implementation area, and is eligible, based on their age and date of birth, to have received the RTS,S/AS01 vaccine, who was admitted with **probable or confirmed meningitis**, defined as:
 - Probable meningitis: Children will be considered to have “probable meningitis” if in a suspected case, the macroscopic aspect of the CSF is turbid, cloudy or purulent; or the CSF leukocyte count is >10 cells/mm³.
 - Confirmed meningitis is any suspected or probable case, laboratory confirmed by culture or PCR to be of bacterial, viral or other aetiology in the CSF.
- **Suspected meningitis:** A child with one or more of the following present (with or without fever): neck stiffness, two or more seizures in the last 24 hours, bulging fontanelle, convulsions (partial, complex febrile or other atypical presentations), seizures if less than 6 months or greater than 6 years, altered consciousness (Blantyre Coma Score <3 or, Glasgow Coma Score <11 or P or U on the AVPU scale [Alert Verbal Painful Unresponsiveness Scale]) or any other clinical symptoms indicative of meningitis or cerebral malaria by clinical judgement.
- **Severe malaria:** A case of severe malaria will be defined as a child who resides in an RTS,S/AS01 implementation area, and is eligible, based on their age and date of birth, to have received the RTS,S/AS01 vaccine, who was admitted with severe malaria defined as:
- ***P.falciparum* infection** detected by RDT (antigenaemia detected by RDT or in the absence of RDT result, parasitaemia by microscopy at any density) AND one or more of the following: a) impaired consciousness (Glasgow coma score <11 , OR Blantyre coma score <3 , OR assessed as P or U on the AVPU score) and *not positive* for probable or confirmed meningitis; b) multiple of atypical convulsions (more than two episodes within 24 hours or prolonged (>15 minutes), or focal) and *not positive* for probable or confirmed meningitis; c) respiratory distress (manifested as chest indrawing or deep breathing); d) severe malaria anaemia (haemoglobin concentration <5 g/dL or haematocrit $<15\%$).
- **Deaths:** Children who died from any cause excluding deaths due to accident or trauma, who resided in an RTS,S/AS01 implementation area and who were eligible to have received RTS,S/AS01 vaccine based on their age when they died and their date of birth.

Data collection

- Expected sample size across 3 countries:
 - 46 cases of meningitis
 - 1230 cases of severe malaria
 - 100 cases of cerebral malaria
 - 700 deaths,
and
 - Four (4) controls for each case $\approx$ 8304 controls
- Ethical approvals obtained (Ghana, Kenya, Malawi, LSHTM, WHO)
- Data collection started: **18 October 2021**

Identification of cases (confirmed malaria, microscopy)

- List generated weekly from main MVPE data using an algorithm to ensure diagnostic criteria are followed in selection of cases.
- Cases are visited at home:
 - to confirm details recorded in sentinel hospitals
 - to collect further information about case child and their household
 - field staff recruit controls from the same neighborhood after consent.

Identification of cases: limitations and challenges

- Retrospective visit (no vaccination date)
- Unavailability of vaccination cards/vaccination record
- Difficulty in getting to communities during rainy season
- Mitigated by:
 - Completion of case visits immediately it occurs
 - visit to health facilities for vaccination information
 - caregiver recall of vaccines



**Review of immunization register in a health facility
by field officer**

Identification of controls (without malaria)

- For each type of case, four control children born within 1 month of the date of birth of the case are recruited from the neighborhood of the case's home, after moving a distance of at least 100m from the home of the case.
- Controls for deaths are recruited following completion of the verbal autopsy (VA), the VA team recruit controls from the same neighborhood where the case child was living.

Identification of controls: limitations and challenges

- Difficulty in getting 4 age eligible controls per case
- Large area covered to find controls (5-7 km distance)
- Unavailability of vaccination cards/vaccination record
- Mitigated by:
 - revisits to households to find controls
 - Completion of controls visits immediately found
 - Review of health facility registers for vaccination information
 - caregiver recall of vaccines



Field monitoring visit by WHO/LSHTM

Vaccination status

- For cases and controls, vaccination status is determined:
 - from home-based record (HBR)
 - from clinic registers
 - vaccine history from caregiver recall
- Vaccination status are being determined (with respect to RTS,S/AS01 and other vaccines)

The collage displays various vaccination records used in Ghana:

- MATERNAL AND CHILD HEALTH RECORD BOOK:** A green and red cover with a circular logo.
- GHANA EPI TALLY BOOK:** A form from the Ministry of Health, Ghana Health Service, for recording vaccine status.
- MATERNAL HEALTH RECORD:** A handwritten card for a child named KLUSSY ABRAHAM ABRAHAM, detailing birth date (24/6/18), weight (10.2kg), and vaccination status.
- Immunization and Vitamin A:** A printed form with columns for Age Period, Vaccine, Date Given, Batch No., Place Given, and Date of Next Visit. It includes sections for Other Vaccines, Measles Rubella Vaccine (MR), Yellow Fever Vaccine, and Malaria Vaccine.

Progress and children with vaccination record: Dec. 2022

Outcome	Variable (Ghana, Kenya, Malawi)							
	Cases completed	% Cases with vaccine record seen	% Cases with no vaccine record*	% Traced in health facility register from cases who had no vaccine record	Controls completed	% Controls with vaccine record seen	% Controls with no vaccine record*	% Traced in health facility register from controls who had no vaccine record
Severe malaria	726 (59%)	81	19	1	2853 (58%)	86	14	1
Cerebral malaria	45 (45%)	62	38	2	174 (43%)	80	20	2
Meningitis	19 (41%)	74	26	5	73 (40%)	81	19	1
Mortality	750 (107%)	68	32	2	2959 (106%)	88	12	2
Overall	1540 (74%)	74	26	2	6059 (73%)	87	13	2

*2% of cases and 3% of controls never vaccinated (zero dosed)



Use of caregiver recall in absence of home-based record to assess vaccine coverage

Summary findings:

- Caregiver recall from household surveys (children with home-based record).
- Results:
 - level of agreement/concordance in coverages between recall- and card-based data was high
 - RTS,S coverage levels from recall-based data are higher than card-based data
 - Differences in RTS,S coverage from recall- and card-based data are wider in comparator clusters compared to implementing clusters
 - The results support use of caregiver recall in estimating vaccination coverage as an alternative in the absence of card-based data
- Conclusion: Existing system of caregiver recall or history is reliable to use to assess vaccine coverage

Ethical consideration

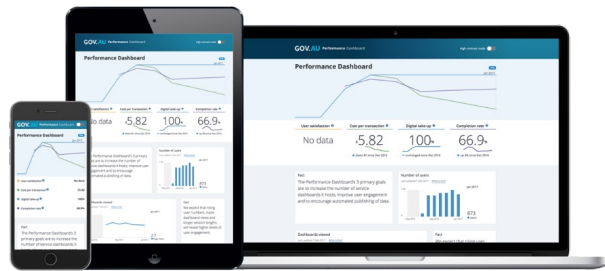
- Consent needed for the MVPE case control studies? Yes, for data collection
- What about programme?



Field officer obtaining an informed consent

Data management/analysis

DATA MANAGEMENT



Near real-time
monitoring



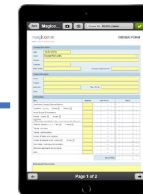
KHRC central online
Secure Server

Store and Forward



Clinical outcomes
data capture

Store and Forward



Mortality outcome
data capture

Analysis

- Analysis of case control approach requires statistical support
- As part of analyses, the data analysis plan (developed) and analysis will be carefully documented to share widely

Next steps

- Develop manual for the case control approach
- Develop budget template to help estimate cost of evaluation
- Support the use of case control approach for monitoring and evaluation of malaria vaccine impact by country programmes
- Participate and organize webinars to disseminate case control approach to evaluation
- Other countries to visit participating countries for practical learnings. Ghana January 2023, Kenya and Malawi by March 2023
- Publication of methodology is underway.

Acknowledgement

- EDCTP
- WHO
- Participating Ministry of Health in Ghana, Kenya, Malawi
- Consortium institutions
- Community members
- TDR

Thank you

