Malaria Vaccine Implementation Programme (MVIP)

Update to MPAC

17 October 2018

World Health Organization

Outline

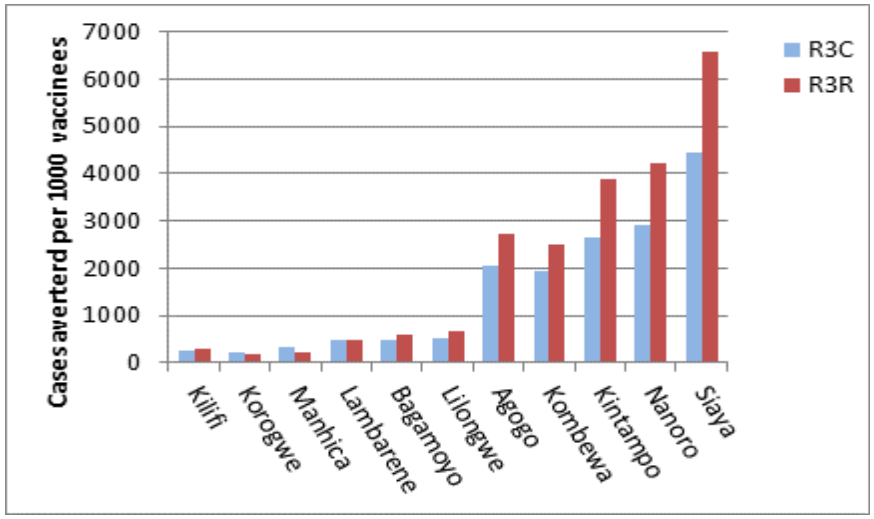
- Brief review of Phase 3 trial results and MVIP
- Mal 076 findings
  - 7 year follow-up of children in the large phase 3 trial (Mal 055) at 3 of 11 sites
- Timeline and targets for vaccine introduction
- Update on Framework for Policy Decision
- Data source for safety endpoints
- Funding for last 2 years of MVIP

RTS,S vaccine efficacy during 48 months follow-up in children first vaccinated at age 5-17 months, 4 doses*

5-17 month age category	4 doses
Clinical malaria	39%
Severe malaria	29%
Severe malaria anaemia	61%
Blood transfusion	29%
Malaria hospitalization	37%

*Efficacy against severe malaria lost without 4th dose.

Vaccine Impact and Safety



- Potential for high impact moderate/high transmission with 4 doses
  - Averted 1000s of cases/1000 children vaccinated over 4 yrs
  - modelled estimates of 1 death prevented/200 vaccinated
- Safety
  - Febrile Seizures
- Potential safety signals (no causal relationship established):
  - Meningitis, cerebral malaria
  - In setting of very low mortality due to study design, *Post-hoc* finding of more deaths among vaccinated vs unvaccinated girls

Regulatory review

- European Medicines Agency (EMA) issued a **positive scientific opinion** under article 58
  - Applying the same rigorous standards as for medicines to be marketed in the EU
  - Stating that the safety profile is acceptable
  - Risk-benefit profile favourable
- NRAs from three pilot countries authorized for use in pilot areas

WHO position and pilot introduction

- Recommended phased introduction in pilot implementations to answer outstanding key questions on
  - Feasibility of reaching children with 4 doses, including a 4th dose at 2 years of age
  - Safety in the context of routine use, emphasis on meningitis and cerebral malaria
  - Impact on mortality (including gender specific) and severe malaria
- **Information from Pilot Evaluations will inform WHO policy on the use of RTS,S vaccine across Africa, in 2023**
- Vaccine will be piloted in Kenya, Malawi, Ghana

Components of the MVIP

1. Sub-national introduction by EPI programme through routine systems
2. Rigorous evaluation
   - Feasibility, safety in routine use, impact
3. GSK-led phase IV observational study
   - Includes enrolled cohort of vaccinated & unvaccinated children
   - Safety, effectiveness and impact
   - Part of GSK risk management plan with EMA
4. PATH-led qualitative assessment/economic analyses

Malaria-076: 7-year follow-up at 3 of 11 sites
Study objectives and design

- Primary objective: describe **severe malaria** incidence
  - Measure **rebound** after RTS,S 3rd dose or 4th dose
- Secondary objectives:
  - Clinical malaria incidence
  - Malaria hospitalisation, fatal malaria, cerebral malaria
  - SAEs (fatal, malaria related, meningitis, pIMD)

Malaria-076: 7-year follow-up at 3 sites
Study objectives and design

- Open label, **long-term follow-up** of children in Mal-055
  - 3 study groups (4 dose, 3 dose, control); two age categories
    - (N =1748)
  - **3 additional calendar years**: Jan 2014 to Dec 2016
    - Phase 3 trial: March 2009 through Dec 2013
  - **3 study sites**: Korogwe (Tanzania), Kombewa (Kenya), Nanoro (Burkina Faso)
- Gap between end Malaria-055 and start Malaria-076 with some **retrospective** data collection prior to prospective :
  - Nanoro 10 months
  - Korogwe 21 months
  - Kombewa 24 months

Vaccine efficacy against **clinical malaria** by follow-up period

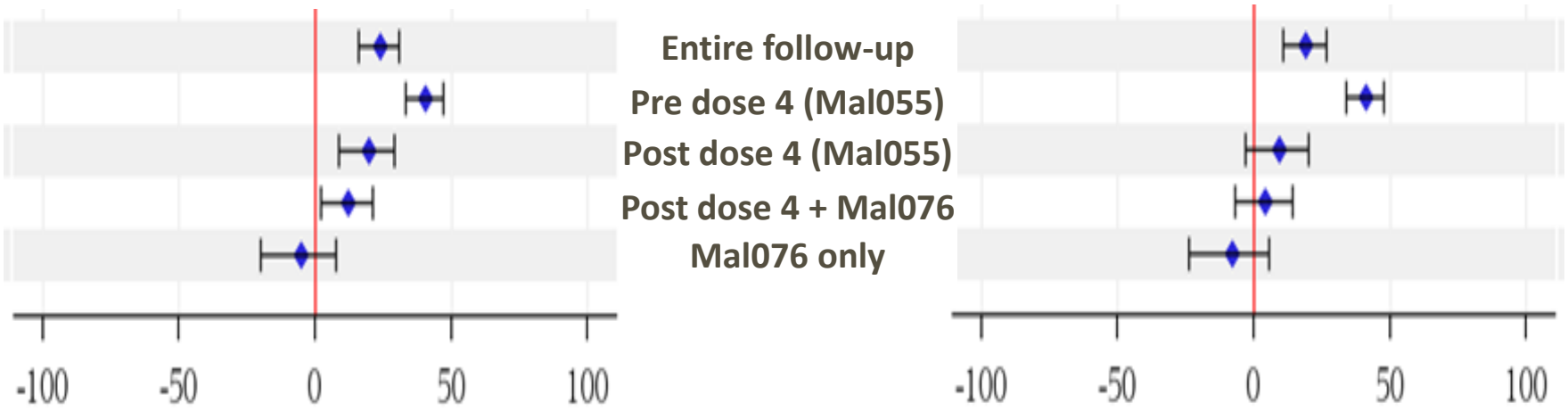
4 doses

7 year: 24% (16, 31)

5-17 months

3 doses

7 year: 19% (11, 27)



Data for the three sites combined

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Vaccine efficacy against **severe malaria** by follow-up period

(case definition 2)

Data for the three sites combined

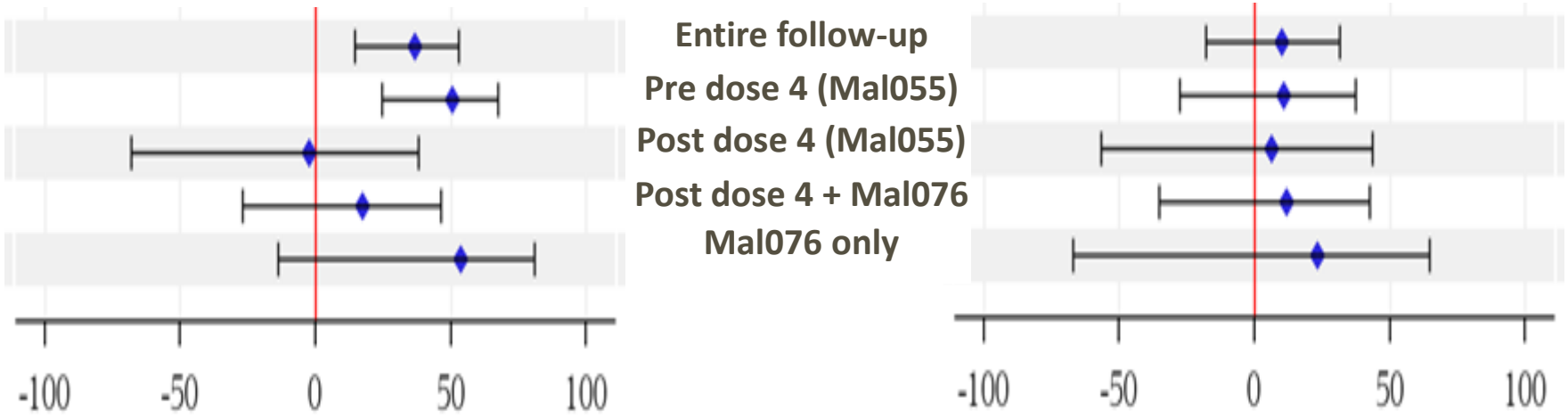
5-17 months

4 doses

7 year: 37% (15, 53)

3 doses

7 year: 10% (-18, 32)



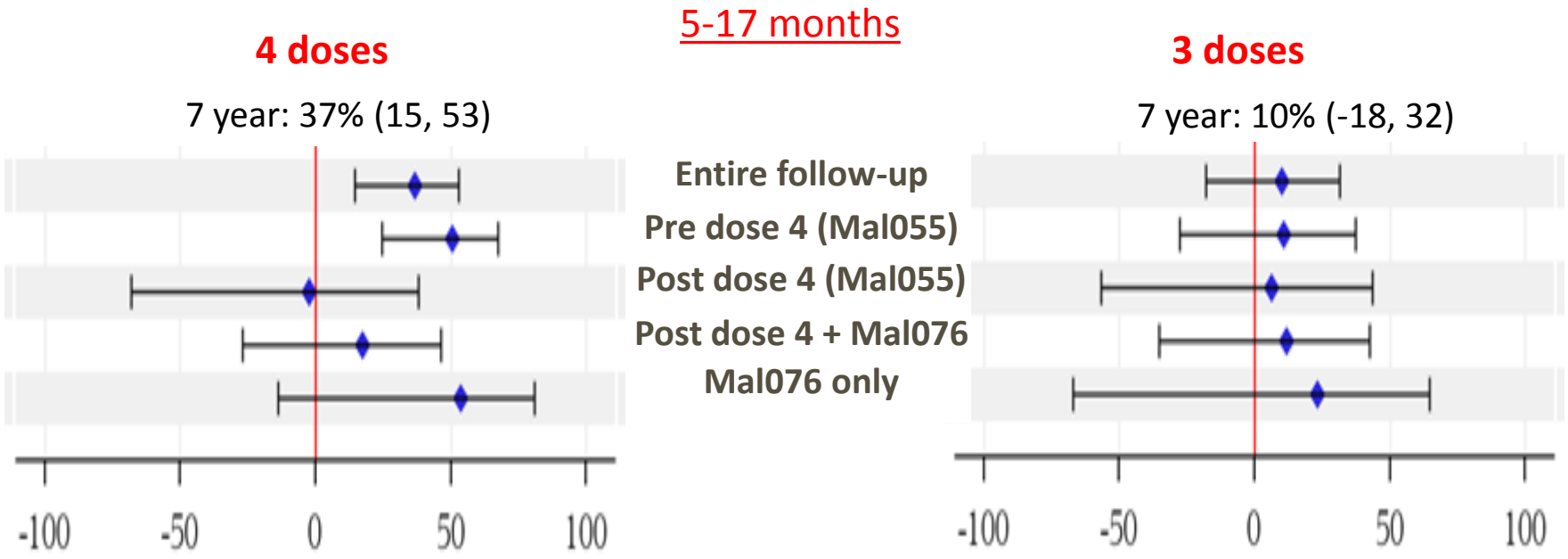
World Health Organization

Vaccine efficacy against **severe malaria** by follow-up period

(case definition 2)

Data for the three sites combined

5-17 months



- Burkina Faso, intensely seasonal: higher incidence clinical malaria compared with controls during last 3 years (Mal 076) in children receiving 3 or 4 doses
- No corresponding higher incidence of severe malaria

Results for severe malaria in study Malaria-076

The numbers in 5-17 months age category

	Group	4 doses RTS,S/AS01			3 doses RTS,S/AS01			Control
	N	594			561			593
Endpoint	Period	n	% VE	(95% CI)	n	% VE	(95% CI)	n
Severe malaria	M0-M20	**32**	50.58	(24.52; 67.65)	**57**	10.61	(-27.6; 37.38)	**65**
(case definition 2)	M21-SE	**31**	-2.28	(-68.3; 37.85)	**28**	6.06	(-56.7; 43.67)	**31**
	Mal-076	**7**	53.68	(-13.7; 81.13)	**11**	23.33	(-67.1; 64.82)	**15**
	Total	**70**	36.69	(14.6; 53.07)	**96**	10.14	(-18.1; 31.64)	**111**

Case definition 2: Case definition 1 **OR** SAE report (within -1 to +3 days of admission) including preferred term of "Malaria", "*P. Falciparum* infection" or "Cerebral malaria"

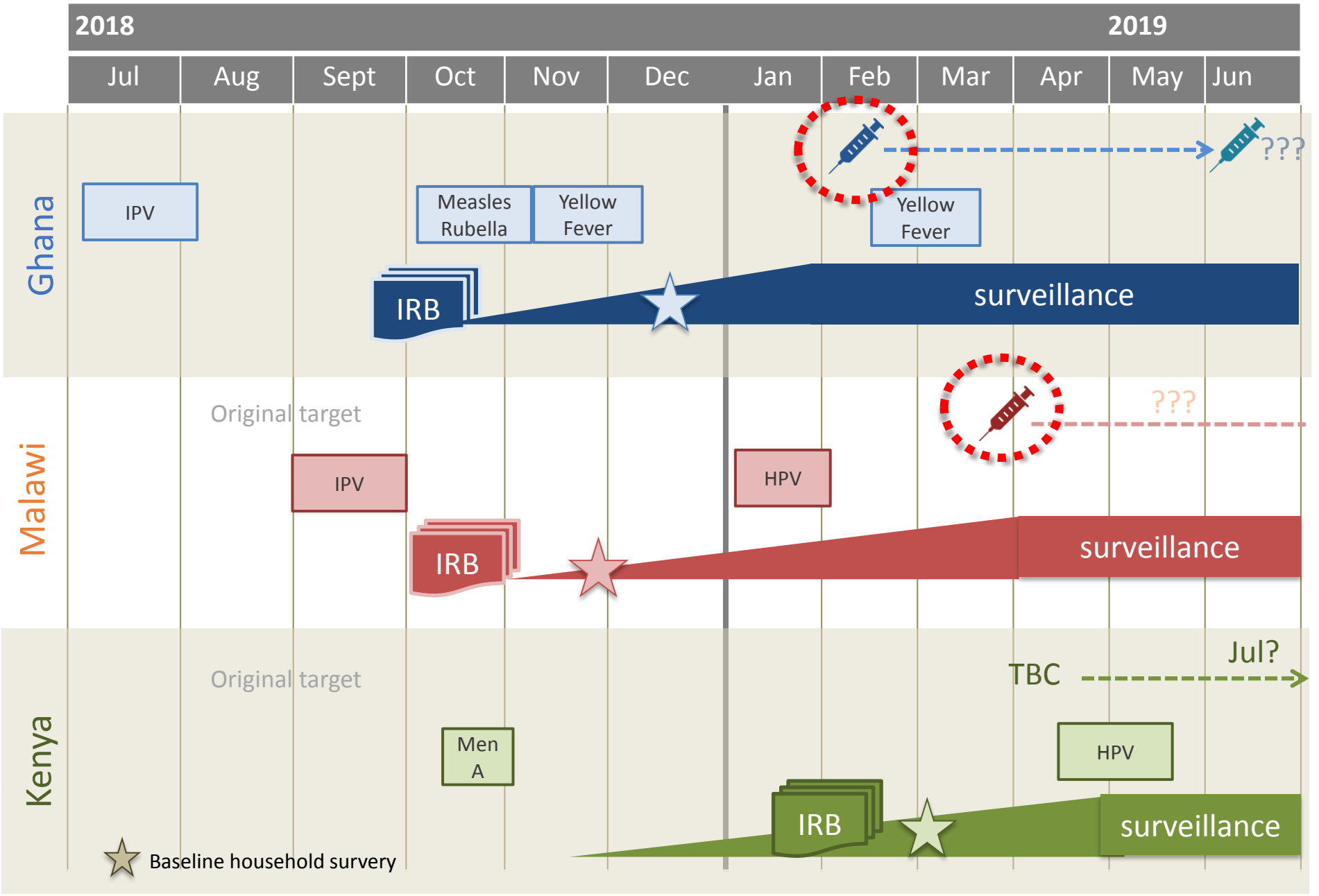
Safety endpoints, 5-17 month age-category

- Deaths during Mal 076
  - 1, 2, 2 in 4 dose, 3 dose, control respectively
- Meningitis
  - 1 case in control group
- No cases of cerebral malaria (in either age category)

Interpretation of Mal-076 results

1. Children living in areas with moderate to high perennial malaria transmission who receive 4 doses of RTS,S
   - Are expected to benefit for at least 7 years after vaccination
   - Do not have an excess risk of clinical or severe malaria
2. Children living in areas with moderate to high perennial malaria transmission who receive only 3 doses of RTS,S
   - Are expected to benefit from protection against clinical malaria for *at least* 18 months after dose 3
   - Do not have excess severe malaria
3. Some settings may experience a limited period of increased risk of clinical malaria
   - 3 doses, intensely seasonal
   - Use of other approaches to control malaria should continue

Current targets for vaccine introduction in 3 pilot countries



MVIP evaluation partners

Ghana	Kenya	Malawi
Kintampo Health Research Centre (KHRC)	**National Foundation for the Centers for Disease Control and Prevention, Inc. (CDC Foundation)**	**The College of Medicine**
Navrongo Health Research Centre (NHRC)	**The U.S. Centers for Disease Control and Prevention (CDC)**	Malawi-Liverpool-Wellcome Trust Clinical Research Programme (MLW)
Research and Development Division (RDD) of Ghana Health Service	The KEMRI-Wellcome Trust Research Programme (KWTRP)	The University of North Carolina Project Malawi (UNCPM)
University of Ghana School of Public Health Malaria Research Centre, Agogo Presbyterian Hospital	The Walter Reed Project (WRP)	
University of Health and Allied Services (UHAS)	The Kenya Medical Research Institute (KEMRI)	
Noguchi Memorial Institute for Medical Research		

Framework for policy decision making

- Framework purpose: describe how MVIP feasibility, safety, and impact data on RTS,S will be used to inform policy
- Joint working group of representatives from SAGE, MPAC, PAG, modelers
  - Initial teleconference in July
  - Face to face meeting in 3-4 December
  - Target presentation to SAGE/MPAC in April 2018
    - Preparing background information on inputs to prior policy decisions

Data source for safety indicators

	Sentinel hospital surveillance	Community mortality surveillance	Routine PV	GSK-led Phase IV study
Meningitis & Cerebral Malaria signal	Yes	No	No	Yes
Mortality gender imbalance	No	Yes	No	No
Rare, temporally related events	Yes, but few	No	Yes	Yes
Rebound	No	No	No	No

MVIP funding:

- Fundraising for phase 2 beginning now
- Essential to avert a gap in funding between Phase 1 (2017-2020) and Phase 2 (2021-2022)
  - Disruption could jeopardize entire programme
  - Discussions with GF required prior to year end
  - GAVI discussions initiated
  - May be difficult for Boards to consider additional funding while vaccinations have not yet begun

Key milestones achieved since 2017:

- MOH engaged – pilot areas selected, introduction plans developed, introduction activities underway
- Collaboration agreement WHO/PATH/GSK signed
- Advisory bodies set up, convened
- Communication, including launch plans developed
- Training materials developed, adaptation
- Regulatory approval for RTS,S secured
- Vaccine supply ready for shipment
- Master protocol approved, country specific develop
- Improvements in routine pharmacovigilance
- Processes underway for delivery of cold chain equipment, devices and vaccines
- Key staff hired or recruitment underway
- Evaluation partners identified, contracted
- Etc…

Chronology of key milestones in the Malaria Vaccine Implementation Programme (MVIP)

Last updated: September 2018

	Cross-cutting	Vaccine implementation	Pilot evaluation
2015	• Oct: SAGE/MPAC recommend pilot implementation of RTS,S	• Dec: WHO issues a call for expression of interest to take part in the MVIP	
2016	• Jan: First WHO Malaria Vaccine Position Paper published • Apr: Funding proposal submitted to Gavi and Unitaid • Jun: Gavi commits up to $27.5m for Phase 1 contingent on equivalent contributions by others • Jun: Unitaid approves 'strategic fit' • Sep: Unitaid commits $9.6m for Phase 1 and $3.6m for Phase 2 • Sep: PATH provides bridge funding to WHO to start MVIP activities • Nov: Global Fund approves $15m for Phase 1 from its 'catalytic funds'	• Jan: Ministries of Health from 10 countries express interest to take part in the MVIP • Oct-Nov: First MVIP visits to Ghana, Kenya and Malawi to present Programme	• Jan: Expert consultation on evaluation design • Jul: First draft of the evaluation protocol
2017	• Feb: First full-time staff for MVIP hired at WHO • Apr: Pilot countries announced by RD • June: Unitaid authorizes its contribution for Phase 1 • Aug: First meeting of the Strategic Access Task Force • Oct: MVIP Collaboration Agreement between WHO, PATH and GSK signed • Dec: Bilateral funding agreements for Phase 1 signed between WHO and Gavi, Global Fund and Unitaid	• Mar: Following confirmation of funding, second MVIP visits to Ghana, Kenya and Malawi to continue planning • Jun: First draft vaccine introduction plan developed by Ghana EPI • Jul: First draft vaccine introduction plan developed by Malawi EPI • Oct: First draft vaccine introduction plan developed by Kenya NVIP • Oct: First meeting of the Programme Advisory Group (PAG) for the MVIP	• May: Request for Proposals to identify evaluation partners published by WHO • July: Draft evaluation master protocol submitted to WHO Ethics Review Committee (ERC) • Sept: WHO Contract Review Committee (CRC) endorses shortlist of bidders for further negotiations • Oct: PATH selects its partners for the qualitative Healthcare Utilization study • Oct: Summary submission to EMA (as part of GSK's RMP) of v6.1 of the evaluation master protocol • Nov: Meeting with prospective evaluation partners at ASHTM to advance negotiations
2018	• Jan: First disbursement of MVIP funds to WHO • Apr: First comprehensive public presentation on MVIP at MIM • Apr: Comprehensive MVIP update to SAGE • Jul: Funders approve WHO budget reprogramming request	• Feb: Joint regulatory review facilitated by AVAREF • Feb: Generic RTS,S Information, Education and Communication materials made available to country teams	• Feb: ERC approves evaluation master protocol • May: Request for Proposals to identify External Monitoring Partners published by WHO • Jul: CRC approves selection of evaluation partners for Ghana and Kenya