Joint SAGE and MPAG session on the RTS,S/AS01 malaria vaccine
06 October 2021

Credit: WHO/F.Combrink
Opening remarks

Kate O’Brien, Director IVB, WHO
Pedro Alonso, Director GMP, WHO
Alejandro Cravioto, Chair of SAGE
Dyann Wirth, Chair of MPAG
Introduction to the session: Framework for WHO recommendation on RTS,S/AS01 malaria vaccine and summary findings

Kim Mulholland, Member of SAGE and the RTS,S Working Group
Objectives

• To present SAGE and MPAG with updated evidence on feasibility, impact and safety of the RTS,S/AS01 malaria vaccine and the proposed recommendations of the RTS,S SAGE/MPAG Working Group.

• SAGE and MPAG are requested to address the following question:

  Does the additional evidence on the feasibility, safety and impact of the RTS,S/AS01 vaccine support a WHO recommendation for use of the vaccine in children in sub-Saharan Africa beyond the current pilot implementation?
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Joint SAGE/MPAG session on RTS,S/AS01 Malaria Vaccine
RTS,S SAGE/MPAG Working Group members

Prof Ifedayo Adetifa  
KEMRI-Wellcome Trust Research Programme, Kenya

Dr Corine Karema  
Independent consultant (and former Director of the Rwanda National Malaria Control Programme), Rwanda

Prof Kim Mulholland  
Murdoch Children’s Research Institute, Australia

Prof Peter Smith  
London School of Hygiene & Tropical Medicine, United Kingdom (Chair)

Dr Dafrosa Cyrily Lyimo  
Independent consultant (and former National Immunization and Vaccine Development Programme Manager), Tanzania

Prof Nick Andrews  
Public Health England, United Kingdom

Dr Eusebio Macete  
Centro de Investigação em Saúde de Manhiça, Mozambique (Co-Chair)

Prof Kathleen Neuzil  
Center for Vaccine Development and Global Health (CVD), University of Maryland School of Medicine, USA

Prof S. Patrick Kachur  
Mailman School of Public Health, Columbia University, USA

Previous members
The late Ms Adelaide Shearley  
Prof Frederick Were  
Prof Graham Brown  
Dr Dominique A. Caugant  
Prof Francine Ntoumi

Joint SAGE/MPAG session on RTS,S/AS01 Malaria Vaccine

See biographies for additional affiliations and areas of expertise
Framework for WHO recommendation on RTS,S/AS01 - Endorsed by SAGE & MPAG in April 2019

Step-wise approach to guide how and when data collected through the MVIP can inform WHO recommendations on use of RTS,S/AS01 beyond the pilots.

• Aim to ensure a recommendation is made as soon as risk-benefit of the vaccine can be established with the necessary level of confidence, such that the vaccine would not be unnecessarily withheld from countries in need, if it is found to be beneficial.

• Recommendation would not be predicated on attaining high coverage, including dose 4 coverage.
Since 2015 new data have alleviated previous concerns around the 4th dose

1. An extended follow-up study of subset of children from the Phase 3 trial (2009 – 2014) showed that over a total of 7 years follow-up*:
   - Any rebound was time limited with no excess severe malaria after 3 dose regimen
   - No rebound after 4 dose regimen
   - MPAG reviewed data and concluded that benefit was greater after 4 doses, but 3 doses were also beneficial

2. Mathematical modeling (SwissTPH, Imperial) indicate most benefit is gained by reaching high coverage with the first 3 doses, with 4th dose providing marginal added benefit when considered on a population level over time

3. Attaining high vaccine coverage takes time, especially with vaccines administered in the second year of life. Would not want to unduly delay introduction of a vaccine that can be life-saving

*Tinto et al, LID 2019
Summary findings from the MVIP

1. Feasibility: Vaccine introduction is feasible, with good coverage of first 3 doses through the routine systems, no impact on uptake of other vaccines, insecticide-treated bed nets (ITNs), care-seeking behavior

2. Safety: No evidence in the pilot evaluations that the safety signals that were seen in the phase 3 trial were causally related to the RTS,S vaccine (meningitis, cerebral malaria, female deaths compared with male deaths)

3. Impact: Vaccine introduction resulted in a statistically significant 30% reduction in hospitalized severe malaria and 21% reduction in hospitalization with malaria infection

4. Additional evidence: A recent Phase 3 trial of RTS,S vaccine provided just before the peak transmission season provides additional evidence of impact and indicates possible flexibility that countries could use in introducing the vaccine
Malaria burden and the need for new interventions

David Schellenberg, WHO
Malaria disease context: Progress has plateaued and new tools needed

Number of malaria cases global and WHO Africa Region, 2000 - 2019

Highest Burden in Africa (2019)
- 215 Million cases (94% in Africa)
- 384,000 Deaths (94% in Africa)
- 265,000 deaths from malaria in African children

Source: WHO estimates, World Malaria Report 2020
Recommended tools to prevent malaria in children, layered for highest impact

Coverage estimates for 2019 in sub-Saharan Africa

**Insecticide treated nets (ITN)**
- 52% of children under age of 5 sleeping under ITNs
- Efficacy:
  - 45% reduction uncomplicated malaria
  - 45% reduction severe malaria
  - 17% reduction U5 all-cause mortality

**Indoor residual spraying (IRS)**
- 2% of populations at risk protected by IRS
- Efficacy:
  - 14% reduction uncomplicated malaria

**Intermittent preventive treatment in infants (IPTi)**
- Implemented only in Sierra Leone
- Efficacy:
  - 27% reduction in clinical malaria

**Seasonal malaria chemoprevention**
- 21 million children reached with at least one dose of SMC in 13 countries with highly seasonal malaria
- Efficacy:
  - 74% reduction uncomplicated malaria
  - 73% reduction in severe malaria


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Sub-national stratification of malaria control

Illustration for Ghana - Intervention targeting (CM and IPTp everywhere)

Intervention mixes

IRS
LLINs (with urban microstratification)
PBO + new nets
SMC

Guiding principle: Legitimacy
Make global decisions about vaccine allocation through transparent processes that are based on shared values, best available scientific evidence, and appropriate representation and input by key parties.

Framework for allocation of limited supply
Proposed process for development

1. Market dynamics: Level of supply availability
2. Learning from experience
3. Scientific & public health considerations: How to maximize benefit?
   - Based on principles on the use of the vaccine within the current mix of malaria interventions
4. Implementation considerations
   - Readiness
   - Acceptance / Political feasibility
5. Social values
   - Fairness / reciprocity
   - Equity / Access

Are any additional inputs needed?

Outputs:
1. Define objectives, principles & required inputs
2. Consensus on allocation framework

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Background on the Malaria Vaccine Implementation Programme (MVIP)

Mary Hamel, WHO IVB
The RTS,S malaria vaccine development: 30-years and counting…

Discovery

Pre-clinical

Phase 1

Phase 2

Phase 3

Malaria Vaccine Implementation Programme

1984

1987

1995
First clinical tests 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 seven African countries

2015
Phase 3 final results published

2015
EMA positive scientific opinion granted

2016
WHO recommendation for pilot implementation

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

RTS,S technical briefing for SAGE and MPAG
2009-2014 Phase 3 trial results

Key outcomes for a 4-dose schedule among children first vaccinated at 5-17 months of age; 4 years of follow-up

**Efficacy:**

- **39%** Reduction in clinical malaria
- **29%** Reduction in severe malaria
- **37%** Reduction in malaria hospitalization
- **62%** Reduction in severe malaria anaemia
- **29%** Reduction in need for blood transfusion

*Efficacy achieved was on top of the benefits provided by insecticide treated bednets*

**Safety:** well tolerated; febrile convulsions

3 Safety signals identified: without established causality

**Modeling:** estimated 1 life saved for every 200 children vaccinated

High impact in Phase 3 trial

Clinical malaria cases averted in Phase 3 trial, 3 or 4 doses in children 5-17 months, by study site and transmission (in the context of high ITN use and facilitated access to good care)

Thousands of clinical malaria cases averted over 4 years with 3 or 4 doses; highest impact in moderate to high transmission areas.

Recognizing potential for high impact, outstanding questions on the vaccine in a real-life setting, recommended pilot phased introduction.

1. **Feasibility**
   - Reaching children with 4 doses
     - Novel schedule: 3 doses monthly; 4th dose ~ 2 years
     - Impact on uptake of other child health interventions (ITN, vaccines, health seeking)

2. **Safety**, with emphasis on signals seen in Phase 3 trial
   - DSMB, EMA considered possible chance findings: no temporal association, inconsistent across sites, no biological model; not seen in pooled analysis of Phase 2 trials (n~2000).
   - 5-17 month only:
     - meningitis,
     - cerebral malaria, post hoc
   - Combined age-categories:
     - Excess female deaths post hoc

3. **Impact** in routine use

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Malaria Vaccine, WHO position paper, https://www.who.int/wer/2016/WER9104.pdf?ua=1
Meningitis: safety signal in Phase 3 trial considered possible chance finding*

- Higher risk limited to children in the 5-17m age-category only
- No temporal clustering; cases > 1000 days after vaccination
- No increase after 4th dose
- Unusually low number of cases in control arm

Source: Mendoza et al, HV&I, 2019

*Joint SAGE/MPAG session on RTS,S/AS01 Malaria Vaccine
Meningitis: safety signal in Phase 3 trial considered possible chance finding*

- Cases clustered by site
- Variety of pathogens: Bacterial, 1 viral, no pathogen isolated
- No known causality model
A Phase 3 trial of seasonal malaria vaccination with or without seasonal malaria chemoprevention (SMC)

- Burkina Faso and Mali (highly seasonal malaria)
- Primary results after 3 annual transmission seasons published in NEJM in August 2021
- Placebo controlled trial
- 6000 children 5-17 months of age
- 3 study groups: ~1000 children per group per country
  1. RTS,S/AS01 given just before high transmission season
  2. 4 SMC courses per year given during high transmission (SMC efficacy ~75%)
  3. Combined SMC and seasonal RTS,S
- All children given an LLIN at enrolment

Summary results

• **Seasonal vaccination non-inferior to 4 rounds of SMC:**
  • Compared to SMC with 4 cycles per year, RTS,S provided non-inferior protection against clinical malaria in Burkina Faso and Mali

• **Combined intervention of RTS,S and SMC is superior to either alone**
  • ~60% reduction in primary outcome of clinical malaria
  • ~70% reduction in WHO-defined severe malaria hospitalisations
  • ~60% reduction in blood transfusions
  • ~50% reduction in all cause deaths, excluding injuries and surgery
  • ~70% reduction in deaths from malaria

• Efficacy did not vary strongly by study country
• No evidence of safety signals seen in Phase 3 trial 2009-2014
MVIP is a collaboration across many partners

Evaluation partners
Commissioned by WHO

Ghana

Kenya

Malawi

Funders

External monitor

Reference laboratories

Partners qualitative study
Commissioned by PATH
Four components of the MVIP

1. **RTS,S/AS01 Implementation through EPI Programme**
   - In selected areas of Ghana, Kenya & Malawi

2. **Pilot evaluation commissioned by WHO**
   - Incl. sentinel hospitals surveillance; community-based mortality surveillance; 3 household surveys

3. **Qualitative assessment (HUS) & economic analyses**
   - commissioned by PATH

4. **GSK Phase IV study**
   - Safety, effectiveness and impact
   - Part of GSK’s EMA Risk Management Plan

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MVIP areas

Malawi

Ghana

Kenya

11 districts

81 districts in 7 regions

51 sub-counties in 8 counties

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Data Source: MoH Kenya; MoH Malawi; MoH Ghana. Map Production: WHO GIS Centre for Health, DNA/DDI. © WHO 2021. All rights reserved.
Review by expert advisory bodies, 2021

- **30 April**: Pilot Evaluation data lock for 24-month primary analysis
- **27-28 July**: Review by MVIP DSMB of safety and impact analysis
- **9 Aug**: Review by African Advisory Committee on Vaccine Safety (AACVS)
- **10 Aug**: Review by Global Advisory Committee on Vaccine Safety (GACVS)
- **1 July**: RITAG update
- **5 & 11 May**: Technical briefings for SAGE & MPAG
- **2 or 8 Sept**: Technical briefings for SAGE & MPAG
- **24-26 August**: Full evidence review by RTS,S SAGE/MPAG Working Group
- **6 October**: Joint SAGE & MPAG review
Malaria vaccine implementation programme on track despite COVID-19

As of September 2021

>2.3 million vaccine doses administered

>800,000 children received at least one dose

Malawi 23 April

Kenya 13 Sept

Ghana 30 April

Estimates as of 30 Sep 2021 - based on monthly MOH/EPI administrative data reports until Jul 2021 and MVIP team projections for August & September 2021
**Immunization coverage: administrative data reports in MVIP areas**

**Malawi**
- **Penta-3**: 95% (2020) - 100% (May-Jul)
- **RTS,S-1**: 88% (2020) - 91% (May-Jul)
- **RTS,S-3**: 73% (2020) - 78% (May-Jul)

Dose 3 to 4 drop-out: ~19% (after 11 months)

**Ghana**
- **Penta-3**: 92% (2020) - 91% (May-Jul)
- **RTS,S-1**: 71% (2020) - 76% (May-Jul)
- **RTS,S-3**: 66% (2020) - 74% (May-Jul)

Dose 3 to 4 drop-out: ~30% (after 10 months)

**Kenya**
- **Penta-3**: 72% (2020) - 92% (May-Jul)
- **RTS,S-1**: 69% (2020) - 80% (May-Jul)
- **RTS,S-3**: 60% (2020) - 73% (May-Jul)

Dose 3 to 4 drop-out: ~58% (after 5 months)

Stock outs due to delayed shipment (COVID-19 related)

Health worker strikes

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Outstanding question 1: Feasibility
Malaria vaccine implementation experience

Rose Jalang’o, National Vaccines and Immunization Programme, Ministry of Health, Kenya

Credit: WHO/Neil Thomas.
Malaria Vaccine Implementation Program: Kenya’s experience

Dr. Rose Jalang’o
National Vaccines & Immunization Program, Kenya
Preparing for the Malaria vaccine introduction in Kenya

Following 2016 WHO recommendation for the pilots, availability of funding and country selection announcements, MoH Kenya and partners organised into subcommittees:

- Planning and coordination
- Supply and logistics
- Training
- Monitoring and evaluation
- Advocacy and social mobilisation

in partnership with target counties to prepare for malaria vaccine introduction in Kenya
Malaria vaccine introduction in Kenya

• Malaria vaccine (MV) introduced into national routine immunization programme:
  • In 8 high burden counties¹
  • In 26 selected Sub-Counties (purple on map)
  • 603 implementing facilities
  • Annual target of 143,388 children (monthly – 11,949)
  • First child vaccinated on 13th September 2019

¹ Bungoma, Vihiga, Kakamega, Busia, Kisumu, Homa Bay, Siaya and Migori
First child vaccinated on 13th September 2019 in Ndhiwa - Homabay County by the former Minister for Health, Hon. Sicily Kariuki
New visits provide opportunities:
• catching up missed doses
• integrating other child health services (growth monitoring, vitamin A, deworming)
• strengthening second year of life platform
The vaccine as a complementary malaria control tool

In addition to vaccination, continue to use other methods to protect your child from malaria.

KEY MESSAGES
Malaria is preventable and treatable
- Complete all four doses of malaria vaccine for best protection.
- Ensure your child sleeps under an insecticide treated net every night and throughout the night.
- If the child tests positive for malaria, give the full course of anti-malaria even when your child starts feeling better.
Comparative immunization performance

Expanded age of administration

- RTS,S 1 (at 6 mos)
- RTS,S 3 (at 9 mos)
- RTS,S 4 (at 24 mos)
- Pentavalent 3 (at 14 wks)
- Measles-rubella 1 (at 9 mos)
- Measles-rubella 2 (at 18 mos)
- Monthly Target

Doses administered per month

- MR stockout
- Start of Covid-19
- HCW strike
- HCW strike

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COVID-19 pandemic
• Facilities turned to isolation units
• Fear of visiting facilities
• Restricted movements

Frequent Health Care Worker strike
• County specific
• Nation wide strike
• Closure of health facilities

Floods in Western Kenya
• Displacement of persons
• Migration
• Closure facilities

Knowledge gaps age-eligibility and schedule
• Missed opportunities for vaccination
• Frequent staff turn-over

Key challenges
High vaccine acceptability

Political Good will at all levels

Recovery from HCW Strikes & Covid-19

Strong MOH-Partner collaboration

County Government driven

DHIS2-Monitoring

Areas of success

Joint SAGE/MPAG session on RTS,S/AS01 Malaria Vaccine
Strengthened cold chain system across the implementing counties

Development of national Guidelines on Adverse Events Following Immunization

Strengthened collaboration between the NVIP, PPB and DNMP

Health System Benefits

Capacity building of Health Workers and Community Health Volunteers (CHVs)

Improved inpatient management through standard algorithm in the CIN

Formation and Inauguration of Kenya National Vaccines Safety Advisory Committee

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NVIP: National Vaccines and Immunization Program; PPB: Pharmacy & Poisons Board; DNMP: Division of National Malaria Program; CIN: Clinical Information Network
Malaria vaccine Post Introduction Evaluation: Lessons Learnt

- Vaccine introduced through existing EPI system:
  - Vaccine distribution & storage,
  - MCH service delivery,
  - Waste management,
  - Reporting through DHIS2

- Health worker knowledge on malaria vaccine eligibility is improving

- Acceptance of the vaccine among HCWs & caregivers
  - Perception that vaccine reduces frequency and severity of malaria

- Increased vaccination sessions not perceived as increasing MCH workload.
  - Separate MOH tools for malaria vaccine increased HCW reporting workload

- Use of community outreaches and CHV engagements effective strategies for increasing vaccine uptake
Thank you
Outstanding question 1: Feasibility

Summary of feasibility evidence

Patricia Njuguna, WHO
Midline household survey: feasibility and equity
Methods

Design: Representative cluster sample household (HH) survey, (midline)

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<th>Design</th>
<th>Ghana</th>
<th>Kenya</th>
<th>Malawi</th>
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<tr>
<td><strong>Implementation/comparator</strong></td>
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<tr>
<td>cluster type</td>
<td>District</td>
<td>Sub county</td>
<td>Health facility catchment</td>
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<tr>
<td><strong>Number of clusters</strong></td>
<td>66</td>
<td>46</td>
<td>46</td>
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<tr>
<td>Number of enumeration areas (EA)</td>
<td>264</td>
<td>184</td>
<td>184</td>
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<tr>
<td><strong>Targeted number of households (HH)</strong></td>
<td>6,600</td>
<td>2,600</td>
<td>4,600</td>
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<tr>
<td>Age range (children)</td>
<td>5–48 months</td>
<td>12-23 months</td>
<td>5–48 months</td>
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<td><strong>Data collection</strong></td>
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<tr>
<td>Survey data collection dates</td>
<td>November 2020</td>
<td>May -July 2021</td>
<td>March –April 2021</td>
</tr>
<tr>
<td>Vaccine card availability among children aged 12-23 month (%)</td>
<td>91.1</td>
<td>88.0</td>
<td>88.1</td>
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</table>
Malaria vaccine coverage
Representative household survey data, children 12-23 months (card and recall)

- Good vaccine coverage, approximate the coverage reported from the routine administrative data
- Vaccine uptake in comparator areas low

Source: Midline household survey data from COM Malawi, KHRC Ghana; CDC Kenya
Impact of malaria vaccine introduction on coverage of other childhood vaccines
Representative household survey data, children 12-23 months (card and recall)

- No impact on the uptake of routine vaccinations following the introduction of the malaria vaccine

Source: Midline household survey data from COM Malawi, KHRC Ghana; CDC Kenya
Impact of malaria vaccine introduction on use of insecticide-treated nets (ITN)
Representative household survey data, children 12-23 months (card and recall)

ITN use among children aged 12-23 months prior night %

- No impact on the use of ITN in children following the introduction of the malaria vaccine.
- In Malawi, the decline in ITN use in both the vaccinating and comparator areas from baseline to midline likely due to ITN attrition following last national mass distribution of nets at end of 2018, just prior to baseline survey.

Source: Household survey data from COM Malawi, KHRC Ghana; CDC Kenya
Impact of malaria vaccine introduction on health seeking and care-giving behavior

Representative household survey data, children 12-23 months (card and recall)

- Little to no impact on health seeking behavior or health worker provision of care following the introduction of the malaria vaccine

Source: Household survey data from COM Malawi, KHRC Ghana; CDC Kenya

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Adding a malaria vaccine to current interventions increases access and reduces gaps in malaria preventive tools.

Ghana Midline Feasibility Household Survey Children 12-23 months (conducted in November 2020)

Using insecticide-treated net (69%)
- 63%**
  - 15% use ITN but unvaccinated
  - 55% use ITN and vaccinated

NOT using an ITN (31%)
- 72%*
  - 22% don't use ITN but vaccinated
  - 9% don't use ITN and unvaccinated

Vaccinated with dose 1 of RTS,S (77%)

Source: HHS data from KHRC Ghana
Qualitative study found the RTS,S/AS01 vaccine to be acceptable to both the health service providers and the target population.

The qualitative study showed a strong growth in trust as facilitating vaccine uptake - from initial trust in the health system and vaccines in general to specific trust in the RTS,S/AS01 vaccine.

The qualitative study found a decrease in perceived threats from RTS,S/AS01 and vaccine utilization, corresponding to the growth in trust.

The additional resource requirements for introducing and delivering the vaccine were seen as broadly comparable to other recently introduced vaccines.

Utilizing updated cost estimates, the vaccine is estimated to be cost-effective for perennial transmission settings with greater than 10% PfPr2-10 with an estimated cost per DALY averted of $97 - $103.

Modelling predictions indicate a significant public health impact across a wide range of settings.
### RTS,S cost-effectiveness studies

**Key**
- **Red**: updated estimates based on 3 doses
- **Blue**: estimates based on 4 dose schedule
- **Green**: estimates based on 3 dose schedule
- Lighter shades indicate societal perspective
- Darker shades indicate health system perspective
- Error bars represent the range of estimates, when available

#### World's lowest GDP per capita (2020)

- 97.0
- 103.0
- 80.0
- 87.0
- 136.0
- 200.0
- 187.0
- 98.8
- 115.0
- 109.0

#### Cost per DALY averted (in US$)

- Updated, Swiss TPH 2021
- Updated, Imperial 2021
- Penny et al 2016
- Penny et al 2016
- Galactionova et al 2017
- Sauboin et al 2019
- Sauboin et al 2019
- Seo et al 2014
- Ndekata et al 2021
- Ndekata et al 2021

### Key Points
- All estimates assume a baseline vaccine price of $5 per dose, CE improves with lower assumed vaccine cost.
- Estimated average cost per DALY averted: $80 (range: $44-$279) for a 3-dose schedule, and $87 (range: $48-$244) for a 4-dose schedule, from a health systems perspective - consistent with the 2021 updated CEA estimates (Swiss TPH and Imperial).
Key findings: feasibility, equity, acceptability

• Delivery of the malaria vaccine is feasible:
  • Good vaccine coverage reached within 18 – 24 months- during a pandemic – using routine immunization systems
  • There was no negative impact of vaccine introduction on the uptake of
    • Routine vaccinations,
    • ITN use,
    • health seeking behavior
    • health worker provision of care
• There were no significant disparities in vaccine delivery across sex and SES (data not shown)
• Layering a malaria vaccine to ITNs can broaden reach and reduce gaps in access to malaria prevention tools among vulnerable children
• High acceptability and demand
• Vaccine estimated to be cost-effective in areas of perennial moderate to high malaria transmission
Outstanding question 2: Impact

Summary of impact evidence

Paul Milligan, London School of Hygiene and Tropical Medicine
Results of the RTS,S/AS01 Malaria Vaccine Pilot Evaluation 24 months after the vaccine was introduced: impact outcomes

Paul Milligan, on behalf of the MVPE partnership
Framework for WHO recommendation on RTS,S/AS01 - Endorsed by SAGE & MPAG in April 2019

Step-wise approach to guide how and when data collected through the MVIP can inform WHO recommendations on use of RTS,S/AS01 beyond the pilots.

- Concerns regarding safety signals satisfactorily resolved; and
- Severe malaria or mortality data trends assessed as consistent with a beneficial impact of the vaccine.

If needed: Adjustments to recommendations
### Timing of analyses: number of events required for analyses of safety and impact

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Effect in the phase 3 trial</th>
<th>Population effect if the coverage is:</th>
<th>No. of events required for 90% power</th>
<th>Observed rate/1000</th>
<th>Events to April 2021 (March 2021 for deaths)</th>
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<tbody>
<tr>
<td><strong>Safety</strong></td>
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<td>Meningitis</td>
<td>10.5-fold increase</td>
<td>6.7/7.7</td>
<td>4.5</td>
<td>70-100 &lt;5yrs</td>
<td>0.01-0.06</td>
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<td>Cerebral malaria</td>
<td>2.2-fold increase</td>
<td>1.7/1.8</td>
<td>1.6</td>
<td>300-350 &lt;5yrs</td>
<td>0.1-0.2</td>
</tr>
<tr>
<td>Mortality</td>
<td>2.6-fold relative increase in girls compared to boys (2-fold increase in girls, 0.8-fold in boys)</td>
<td>2.0/2.1</td>
<td>1.8</td>
<td>2500 deaths (among vaccine-eligible)</td>
<td>0.8-2.7</td>
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<td><strong>Impact</strong></td>
<td></td>
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<td>Severe malaria</td>
<td>34% efficacy</td>
<td>20%/24%/19%</td>
<td></td>
<td>4000 &lt;5yrs</td>
<td>0.9-3.9</td>
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</table>

- Combining data for the 3 countries, sufficient events had accrued by April 2021 to address safety signals and to assess effectiveness against hospital admission with severe malaria *in pooled analyses* of data from the 3 countries.

- Therefore, *primary* analysis of these outcomes has been completed based on data to April 2021 (March 2021 for deaths/Verbal Autopsies).
Analysis populations

Hospital and mortality surveillance is maintained for all children 1 to 59 months of age.

Events are classified as eligible to have been vaccinated, or not eligible

The ratio eligible:non-eligible in vaccine areas divided by the same ratio in comparison areas, is an estimate of the incidence rate ratio between vaccine and comparison areas.
Mortality surveillance

• **13,682** deaths in children aged 1-59 months reported to March 31 2021
• **4,729** deaths in vaccine-eligible age groups
  • **95.5%** had Verbal Autopsy completed (or hospital records obtained)
  • **90.5%** had cause of death (injury, or other causes) established

In Malawi

• Possible to estimate population denominators using data from the 2018 census, and then to compare the rates of mortality with mortality estimates from the census.
• Mortality rate in children aged 1-59 months, during the surveillance period, was **4.38/1000** (both sexes combined) (7,359 deaths reported per 1,681,572 person years).
• Similar to national estimate derived from the 2018 census of **5.08/1000**.
Hospital surveillance

• A total of 27,596 patients aged 1-59 months admitted to April 30 2021
  • 13,882 patients from areas where the vaccine implementation areas
    • 4,853 eligible to have received the malaria vaccine based on their date of birth
  • 13,714 patients from comparison areas
    • 5,141 would have been eligible by the same criteria

• Malaria test results were available for 88%.

• A total of 4,338 suspected cases of meningitis investigated
Vaccine delivery & uptake

By April 30 2021:

652,673 children had received their **first** dose of RTS,S/AS01

494,745 children had received their **third** dose

- Household surveys conducted about 20 months after vaccine introduction, in children 12-23 months of age:
  - Received their first dose of RTS,S/AS01:
    - 72.5% in Malawi, 75.0% in Ghana, 78.6% in Kenya
  - Received their third dose:
    - 62.3% in Malawi, 67.0% in Ghana, 62.3% in Kenya

- Similar coverage by wealth rankings based on household assets, and by gender
# Impact among children eligible to have received 3 vaccine doses

<table>
<thead>
<tr>
<th>Number of events in eligible age groups</th>
<th>Implementation areas</th>
<th>Comparison areas</th>
<th>Rate ratio (95%CI)</th>
<th>% impact (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admission with:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>severe malaria</td>
<td>418</td>
<td>689</td>
<td>0.70 (0.54,0.92)</td>
<td>30% (8%,46%)</td>
</tr>
<tr>
<td>cerebral malaria</td>
<td>37</td>
<td>38</td>
<td>0.73 (0.44,1.20)</td>
<td>27% (-20%,56%)</td>
</tr>
<tr>
<td>severe malaria anaemia</td>
<td>131</td>
<td>153</td>
<td>0.78 (0.55,1.09)</td>
<td>22% (-9%,45%)</td>
</tr>
<tr>
<td>Admissions with positive malaria test</td>
<td>1119</td>
<td>1606</td>
<td>0.79 (0.68,0.93)</td>
<td>21% (7%,32%)</td>
</tr>
<tr>
<td>Admission for any cause</td>
<td>3340</td>
<td>3678</td>
<td>0.92 (0.83,1.03)</td>
<td>8% (-3%,17%)</td>
</tr>
<tr>
<td>Mortality due to any cause excl. injury</td>
<td>1421</td>
<td>1443</td>
<td>0.93 (0.84,1.03)</td>
<td>7% (-3%,16%)</td>
</tr>
<tr>
<td>Girls</td>
<td>691</td>
<td>662</td>
<td>0.98 (0.86,1.10)</td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>730</td>
<td>781</td>
<td>0.90 (0.78,1.04)</td>
<td></td>
</tr>
<tr>
<td>Ratio girls:boys</td>
<td>1.08 (0.92,1.28)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Key findings

• Observed impact on hospital admission with severe malaria was consistent with the reduction that would be expected if vaccine effectiveness is similar to that observed in the phase 3 trial, given levels of coverage of 3 doses of RTS,S/AS01 achieved in implementation areas

• No evidence the impact on cerebral malaria differed from that for other forms of severe malaria

• Consistent impact on mortality (with wider uncertainty), but no evidence that impact on mortality differed between girls and boys
Comments & Questions on feasibility and impact
Break
Outstanding question 3: Safety

Summary of safety evidence and assessment by the MVIP Data Safety and Monitoring Board

Cynthia Whitney, DSMB Chair

Credit: WHO/Neil Thomas.
The MVIP Data Safety & Monitoring Board

Dr Cynthia Whitney, Chair
Dr Esperança Seene
Prof Larry Moulton
Prof Charles Newton
Dr Jane Achan

Joint SAGE/MPAG session on RTS,S/AS01 Malaria Vaccine
## MVIP Data Safety & Monitoring Board members

<table>
<thead>
<tr>
<th>Name</th>
<th>Specializations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cynthia Whitney</td>
<td>Epidemiology, Meningitis, Immunization/Vaccines</td>
</tr>
<tr>
<td>Esperança Sevene</td>
<td>Pharmacovigilance (PV), Regional PV systems, Malaria</td>
</tr>
<tr>
<td>Charles Newton</td>
<td>Paediatric neurology, Epidemiology, Cerebral Malaria, Meningitis</td>
</tr>
<tr>
<td>Larry Moulton</td>
<td>Statistics, Epidemiology</td>
</tr>
<tr>
<td>Jane Achan</td>
<td>Epidemiology, Child health, Malaria</td>
</tr>
</tbody>
</table>

Joint SAGE/MPAG session on RTS,S/AS01 Malaria Vaccine
The role of the DSMB is to safeguard the well-being of children participating in the MVIP by regularly reviewing relevant safety data from the pilot evaluations, the GSK-led Phase 4 studies and from routine vaccine pharmacovigilance across the three countries and providing advice and recommendations to WHO.

Since start of the MVIP, convened thirteen times (usually quarterly):

- 6-7 March 2018 (face-to-face)
- 20 June 2018 (virtual)
- 19 September 2018 (virtual)
- 22 January 2019 (virtual)
- 27-28 May 2019 (face-to-face)
- 26 September 2019 (virtual)
- 24-25 November 2019 (face-to-face)
- 3 March 2020 (virtual)
- 7-8 July 2020 (virtual)
- 16 September 2020 (virtual)
- 1-2 December 2020 (virtual)
- 3 March 2021 (virtual)
- 27-28 July 2021 (virtual)

Met quarterly to review indicators of data quality and safety from:
- The MVPE
- Routine national pharmacovigilance systems
- Ongoing GSK-led phase IV study
Reminder: Safety objectives

Assess association of vaccine introduction with increased risk of:

- Mortality among girls compared to boys, all causes except injuries
- Meningitis
- Cerebral malaria, a subset of severe malaria

among children eligible to receive 1 or more doses of RTS,S/AS01 vaccine
Rate ratios for safety endpoints among children eligible to have received 1+ vaccine doses

<table>
<thead>
<tr>
<th>Events in eligible children</th>
<th>Implementing areas</th>
<th>Comparison areas</th>
<th>Rate ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality excluding injuries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>1060</td>
<td>986</td>
<td>0.98 (0.87, 1.09)</td>
</tr>
<tr>
<td>Boys</td>
<td>1091</td>
<td>1143</td>
<td>0.91 (0.80, 1.04)</td>
</tr>
<tr>
<td>Ratio girls:boys</td>
<td></td>
<td></td>
<td>1.08 (0.93, 1.25); p=0.32</td>
</tr>
<tr>
<td>Probable or confirmed meningitis</td>
<td>27</td>
<td>24</td>
<td>0.81 (0.43, 1.55)</td>
</tr>
<tr>
<td>Cerebral malaria (subset of severe malaria)</td>
<td>25</td>
<td>30</td>
<td>0.77 (0.44, 1.35)</td>
</tr>
<tr>
<td>Interaction cerebral vs other severe malaria</td>
<td></td>
<td></td>
<td>0.94 (0.57, 1.56); p=0.81</td>
</tr>
</tbody>
</table>

*ratio of incidence in RTS,S/AS01 implementation areas to that in comparison areas, among children eligible to have received at least 1 dose of the vaccine.
Rate ratio for mortality excluding injury in older children eligible to have received 1+ vaccine doses

Sub-analysis: gender specific mortality in older eligible children (18+ months)

<table>
<thead>
<tr>
<th></th>
<th>deaths in eligible age groups 18+ months old</th>
<th>deaths in non-eligible age groups</th>
<th>Mortality rate ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparison areas</td>
<td>163</td>
<td>1814</td>
</tr>
<tr>
<td></td>
<td>RTS,S/AS01 areas</td>
<td>157</td>
<td>2015</td>
</tr>
<tr>
<td>Boys</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparison areas</td>
<td>181</td>
<td>2060</td>
</tr>
<tr>
<td></td>
<td>RTS,S/AS01 areas</td>
<td>180</td>
<td>2203</td>
</tr>
</tbody>
</table>

Ratio of the mortality rate ratios (girls:boys): 0.95 (0.70, 1.31)
P-value for difference between girls and boys p=0.770

No evidence the impact of RTS,S/AS01 introduction on mortality differs between girls and boys, in children 18-30 months
1. Sufficient events were observed to have 90% power to detect safety signals of the magnitude observed in the phase 3 trial, if they occurred, in pooled analysis (across the 3 MVIP countries)

2. No evidence that RTS,S/AS01 introduction was associated with excess mortality in girls
   - All-cause mortality not significantly different between girls and boys, including after 18 months of age

3. No evidence that RTS,S introduction increased the risk of hospital admission for
   - Meningitis
   - Cerebral malaria, a subset of severe malaria
   - No evidence that vaccine impact was less for cerebral malaria than other forms of severe malaria
The 24-month primary analysis had adequate power (number of events accrued) to exclude associations of a similar magnitude to those observed in the Phase 3 trial, after accounting for observed levels of coverage and contamination on population-level effects.

- DSMB observed that pilot evaluation results indicated comparable burden for meningitis, cerebral malaria, and gender-specific mortality among eligible children living in implementation and comparison areas.
  - Pooled point estimates for safety endpoint risk ratios were consistently near 1 (no association)
  - Results inconsistent with corresponding risk ratios observed in Phase 3 trial
Conclusions from MVIP DSMB

Meeting of 27-28 July 2021

- Safety signals seen in Phase 3 clinical trial (2009-2014) were not observed when the vaccine was scaled up in the MVIP
- Safety signals seen in the Phase 3 trial were not observed in the ongoing GSK sponsored Phase 4 study
- Pilot evaluation pooled results demonstrate effectiveness of RTS,S against severe malaria
- As expected, results were not yet powered to detect impact on mortality
- Based on data reviewed from the national pharmacovigilance (PV) programmes, the DSMB did not find evidence of new conditions that warrant closer safety tracking
In addition to data from the MVPE, findings from other sources did not show a causal relationship of the safety signals seen in the Phase 3 trial

- Pooled safety analysis of Phase 2 trials RTS,S/AS (n~2000) (Vekemans et al, 2013)
- RTS,S/AS01 seasonal vaccination study (~4000 received RTS,S/AS01; Chandramohan et al, 2021)
- RTS,S/AS01 fractional dose trial (794 received RTS,S/AS01; unpublished)

The EMA has maintained a positive scientific opinion and considers the benefit risk profile of the vaccine favorable

- Reviews at least annually, with last evaluation period to March 2020 and past year now under review
Comments & Questions on safety
RTS,S SAGE/MPAG Working Group assessment and proposed recommendations

Peter Smith, RTS,S SAGE/MPAG Working Group Chair
Eusebio Macete, RTS,S SAGE/MPAG Working Group Co-chair
• DSMB concluded safety signals seen in the Phase 3 clinical trial (2009 –2014) were not seen in the pilot implementation

• National pharmacovigilance (PV) programmes and ongoing GSK Phase 4 studies did not show evidence of new conditions that warrant closer safety tracking

• Safety signals seen in the Phase 3 trial have not been observed in:
  - Pooled safety data from Phase 2 trials of RTS,S/AS
  - Trial of seasonal use of RTS,S/AS01 with or without seasonal malaria chemoprevention
  - Trial on fractional dose of RTS,S/AS01
  - Extended follow up study of a subset of children in Phase 3 trial

• The African Advisory Committee on Vaccine Safety (AACVS), the Global Advisory Committee on Vaccine Safety (GACVS), and the Working Group agreed with the DSMB conclusions
RS,S SAGE/MPAG Working Group Assessment: Impact

- DSMB concluded that the MVPE findings demonstrated effectiveness of RTS,S/AS01 vaccine against severe malaria
  - 30% reduction in severe malaria
  - 21% reduction in hospitalization with malaria parasitemia
    - both statistically significant
- The Working Group agreed with the DSMB conclusions
Despite RTS,S/AS01 being a new vaccine delivered through EPI and requiring an expanded schedule, reasonably high coverage of the first three doses was achieved in all three pilot countries— in a relatively short time period and in the context of substantial challenges to the health system due to the COVID-19 pandemic.

Preliminary information on 4th dose suggests drop-out rates between dose 3 and dose 4 have been around 19-30% in Malawi and Ghana (after 9-10 months of implementation).

Insufficient time has passed since dose 4 introduction to assess drop-out rates in Kenya.
Feasibility (cont.):

- Malaria vaccine introduction did not have an impact on the uptake of routine vaccinations, health care seeking behaviours for febrile illness, use of ITNs
- Evidence the malaria vaccine reaches children who may have lower access to and lower use of other malaria prevention measures
- Introduction of the vaccine ensured that access to at least one malaria prevention tool (ITNs or vaccine) was expanded substantially
- Based on qualitative studies conducted as part of the MVIP, care givers and health care providers generally had positive attitudes towards the vaccine
The RTS,S SAGE/MPAG Working Group recommends that RTS,S/AS01 should be provided at a minimum of 4 doses to reduce malaria disease and burden in children from 5 months of age living in countries in sub-Saharan Africa with moderate to high malaria transmission.
• The RTS,S/AS01 vaccine has an acceptable safety profile, and its introduction results in a significant reduction in severe malaria, an acceptable surrogate indicator for the likely impact on mortality
• The vaccine provides substantial added protection against malaria illness and death even when provided in addition to a package of existing interventions which are known to reduce the malaria burden
• The introduction of a vaccine at this time would come when progress in recent years has stalled in malaria control in Africa, when our current tools are threatened by drug and insecticide resistance, and when malaria remains a primary cause of illness and death in African children, with more than 260,000 child deaths from malaria annually
In areas of moderate to high, perennial malaria transmission:

- Vaccine should be provided as a 3-dose primary series, starting from around 5 months of age and with a minimal interval between doses of 4 weeks
  - For children who are delayed in receiving dose 1, vaccination should be started before 18 months of age
  - A fourth dose should be given between about 12 and 18 months after dose 3 (i.e., at around 18 months to 2 years of age), however there can be flexibility to optimize delivery
RTS,S SAGE/MPAG Working Group recommendations (cont.)

In areas with highly seasonal malaria or areas with perennial malaria transmission with seasonal peaks:

- Consideration should be given to the option of providing the RTS,S/AS01 vaccine seasonally, with potential 5-dose strategies including:
  - For all children under 5 years of age who have already completed the 3-dose primary series through routine administration, provide annual dose(s) just prior to the peak transmission season, or
  - For all children 5-17 months of age, give the 3-dose primary series monthly as a “campaign” just prior to the peak transmission season and then in subsequent years provide an annual dose just prior to peak season

Recommendation for possible 5-dose seasonal malaria vaccination strategies based on available data. This trial is continuing with additional doses provided to children up until the age of 5 years, and final results will contribute evidence on vaccine efficacy beyond 5 doses
RTS,S SAGE/MPAG Working Group: additional considerations

- Careful and intentional monitoring for the safety signals seen in the Phase 3 trial, through quality data collection at sentinel hospitals and through community-based mortality surveillance, has revealed no evidence that the safety signals observed in the Phase 3 trial were causally related to the RTS,S/AS01 vaccine.

- Recommend that no special mechanisms be put in place to look for these signals during expansion of vaccine use or adoption by other countries.
WHO should lead the development of a Framework to guide where the initial limited doses of a malaria vaccine should be allocated:

• Through a transparent process that incorporates input by key parties, with appropriate representation and consultation

• To include dimensions of market dynamics, learning from experience, scientific evidence for high impact, implementation considerations, and social values, including fairness, and equity
The MVIP should continue as previously planned for an additional 2 years to measure:

1. Impact of the introduction of RTS,S/AS01 on mortality; and
2. Added benefit of dose 4

- Data collection on severe malaria and safety endpoints should continue
- Any revisions or modifications concerning the recommendation for dose 4 can be made at the end of the pilots
Implementation Considerations and Research Priorities

WHO/F.Combrink
Flexibility in dosing schedules is encouraged

- Countries may want to provide dose 1 slightly earlier than 5 months of age and may want to provide the first 3 doses monthly
- The pilot uncovered situations where the 6,7,9 month schedule caused some confusion
- MoH officials have expressed an interest in providing dose 4 at the same time as MenA or MR, e.g. both at 18 months of age

Vaccination should continue in the MVIP areas implementing RTS,S/AS01, and expand to the pilot evaluation comparison areas as soon as feasible
Implementation considerations

Data on seasonal vaccination supports its use in areas where malaria transmission is highly seasonal

- It may also be appropriate for areas outside of highly seasonal regions where malaria transmission varies substantially by season
- A seasonal strategy may optimize vaccine efficacy in other areas with moderate to high transmission and seasonality
Monitoring and evaluation

Data from the MVPE and other studies show no evidence that the safety signals observed in the Phase 3 trial were causally related to the RTS,S/AS01 vaccine.

- Strengthening of national pharmacovigilance systems is highly desirable to detect unanticipated adverse effects of this vaccine and any other newly introduced vaccines, as well as for vaccines already in use.

- The MVIP will continue to monitor for or collect data on safety and impact, and on the value of the fourth dose through to the end of the programme and in the planned case-control study.

- Based on experience in the three pilot countries, the MVIP will also provide information on how best to achieve coverage of the 4th dose.

- Monitoring and evaluation are encouraged for flexible schedules and implementation strategies, including for seasonal vaccination of RTS,S/AS01.

- Vaccine effectiveness studies are encouraged following widespread introduction.
Research priorities

*Noting none are prerequisite prior to expanded use of RTS,S/AS01 (1) areas with moderate to high malaria transmission with perennial transmission*

- Through the MVIP, continued collection and monitoring of data on safety and impact and on the added benefit of dose 4 through the programme end and in the planned case-control study
- Consider added or synergistic effect of RTS,S/AS01 when given in conjunction with expanded IPTi
- Through planned case-control study, evaluate for any age shift effect of clinical or severe malaria cases in immunized children (relative to controls) after vaccination schedule completed
Research priorities

*Noting none are prerequisite prior to expanded use of RTS,S/AS01*

(2) areas with highly seasonal malaria or areas with perennial malaria transmission with seasonal peaks

- Operations research around the delivery of seasonal vaccine dosing, including around annual pre-season dosing after a primary series given through the routine health clinics in areas of perennial or seasonal transmission
- Further evaluation required to determine how best to deliver the combination of SMC and seasonal malaria vaccination in areas of high malaria burden in areas of highly seasonal malaria and areas of perennial transmission with seasonal peaks
- Safety, immunogenicity, and effectiveness of annual doses beyond dose 5 will be measured in the ongoing seasonal malaria vaccination trial
Research priorities (cont.)

Noting none are prerequisite prior to expanded use of RTS,S/AS01.

(3) both areas (1) and (2):

- Parasite genotype monitoring to detect any emergence of vaccine escape mutants – in context of broader use of RTS,S/AS01
- Co-administration of RTS,S/AS01 with typhoid conjugate, Meningococcal, and inactivated polio vaccines, and other antigens as appropriate
Discussion and formulation of recommendation
Closing remarks

Dyann Wirth, Chair of MPAG
Alejandro Cravioto, Chair of SAGE
Back-up
## RTS,S SAGE MPAG Working Group Recommendations (1/6)

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>JUDGEMENTS</th>
<th>Varies by setting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROBLEM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the problem a public health priority?</td>
<td>No</td>
<td>Uncertain</td>
</tr>
<tr>
<td><strong>BENEFITS AND HARMS OF THE OPTIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are the desirable anticipated effects large?</td>
<td>No</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Are the undesirable anticipated effects small?</td>
<td>No</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Balance between benefits and harms</td>
<td>Favours intervention</td>
<td>Favours comparison</td>
</tr>
</tbody>
</table>

Joint SAGE/MPAG session on RTS,S/AS01 Malaria Vaccine
## RTS,S SAGE MPAG Working Group Recommendations (2/6)

### CRITERIA

#### BENEFITS AND HARMS OF THE OPTIONS

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>JUDGEMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the overall quality of this evidence for the critical outcomes?</td>
<td>No included studies, Very low, Low, Moderate, High</td>
</tr>
<tr>
<td>Effectiveness of the intervention</td>
<td></td>
</tr>
<tr>
<td>Safety of the intervention</td>
<td>Yes</td>
</tr>
</tbody>
</table>

#### VALUES AND PREFERENCES

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>JUDGEMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>How certain is the relative importance of the desirable and undesirable outcomes?</td>
<td>Important uncertainty or variability, Possibly important uncertainty or variability, Probably no important uncertainty or variability, No important uncertainty or variability, No known undesirable outcomes</td>
</tr>
</tbody>
</table>
## RTS,S SAGE MPAG Working Group Recommendations (3/6)

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>VALUES AND PREFERENCES</th>
<th>JUDGEMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?</td>
<td>No □</td>
</tr>
<tr>
<td>RESOURCE USE</td>
<td>Are the resources required small?</td>
<td>No ☒</td>
</tr>
<tr>
<td></td>
<td>Cost-effectiveness</td>
<td>No □</td>
</tr>
</tbody>
</table>
### RTS,S SAGE MPAG Working Group Recommendations (4/6)

#### CRITERIA

<table>
<thead>
<tr>
<th>EQUITY</th>
<th>What would be the impact on health inequities?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRITERIA: Increased</td>
</tr>
<tr>
<td></td>
<td>☐</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACCEPTABILITY</th>
<th>Which option is acceptable to key stakeholders (Ministries of Health (MoH), Immunization Managers)?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRITERIA: Intervention</td>
</tr>
<tr>
<td></td>
<td>☒</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACCEPTABILITY</th>
<th>Which option is acceptable to target group?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRITERIA: Intervention</td>
</tr>
<tr>
<td></td>
<td>☒</td>
</tr>
</tbody>
</table>
### RTS,S SAGE MPAG Working Group Recommendations (5/6)

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>JUDGEMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEASIBILITY</td>
<td></td>
</tr>
<tr>
<td>Is the intervention feasible to implement?</td>
<td>No ☐</td>
</tr>
</tbody>
</table>

Joint SAGE/MPAG session on RTS,S/AS01 Malaria Vaccine
## RTS,S SAGE MPAG Working Group Recommendations (6/6)

<table>
<thead>
<tr>
<th>Balance of consequences</th>
<th>Undesirable consequences clearly outweigh desirable consequences in most settings</th>
<th>Undesirable consequences probably outweigh desirable consequences in most settings</th>
<th>The balance between desirable and undesirable consequences is closely balanced or uncertain</th>
<th>Desirable consequences probably outweigh undesirable consequences in most settings</th>
<th>Desirable consequences clearly outweigh undesirable consequences in most settings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☒</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of recommendation</th>
<th>We recommend the intervention We suggest considering recommendation of the intervention</th>
<th>We recommend the comparison</th>
<th>We recommend against the intervention and the comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>☒</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>☐ Only in the context of rigorous research</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td></td>
<td>☐ Only with targeted monitoring and evaluation</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td></td>
<td>☐ Only in specific contexts or specific (sub)populations</td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

Joint SAGE/MPAG session on RTS,S/AS01 Malaria Vaccine
# Global malaria vaccine pipeline (active reporting)

<table>
<thead>
<tr>
<th>Translational projects</th>
<th>Vaccine candidates</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1a</td>
<td>Phase 2a</td>
<td>Phase 1b</td>
</tr>
</tbody>
</table>

- **ME-TRAP subunit**
- **Rh5.1/AS01B**
- **Pfs-25, Pfs-28**
- **Pfs-230, Pfs 48/45**
- **RTS,S/AS01E, EPI-MAL-003**

- **rCSP/AP10-602 [GLA-LSQ]**
- **VMP001/AS01B**
- **BK-SE36**
- **FxRTS,S/AS01**
- **R21/MM: Seasonal/EPI**

- **PfCELTOS**
- **PvDBP**
- **Pfs-25 in Pf-infected adult**
- **Pfs230, Pfs 48/45**

- **FMP013/FMP014 ALFQ**
- **Pvs25H/Alhydrogel**
- **RTS,S/AS01E in Pf-infected adult**

- **Chemically attenuated parasite**
- **PvSPZ**
- **R21/MM: Seasonal/EPI**

- **Genetically attenuated parasite**

- **Rh5.1/Matrix M**
- **PvSPZ**
- **Pfs230, Pfs 48/45**

### Vaccines
- **Pre-erythrocytic**
- **Blood stage**
- **Transmission-blocking**
- **Pregnancy**

- **P. falciparum**
- **P. vivax**

---

Last updated 16 Aug 2021 based on ClinicalTrials.gov and WHO Rainbow Table

Joint SAGE/MPAG session on RTS,S/AS01 Malaria Vaccine
Meningitis

<table>
<thead>
<tr>
<th>Country</th>
<th>Vaccinating Year</th>
<th>Age-eligible cases</th>
<th>Age-ineligible cases</th>
<th>Rate ratio</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghana</td>
<td>MAY2019-APR2021</td>
<td>8</td>
<td>12</td>
<td>.</td>
<td>0.67 (0.15, 3.04)</td>
</tr>
<tr>
<td>Kenya</td>
<td>SEPT2019-APR2021</td>
<td>14</td>
<td>19</td>
<td>.</td>
<td>0.57 (0.22, 1.45)</td>
</tr>
<tr>
<td>Malawi</td>
<td>MAY2019-APR2021</td>
<td>5</td>
<td>13</td>
<td>.</td>
<td>1.73 (0.48, 6.24)</td>
</tr>
<tr>
<td>Pooled</td>
<td>MAY2019-APR2021</td>
<td>27</td>
<td>44</td>
<td>.</td>
<td>0.81 (0.43, 1.55)</td>
</tr>
</tbody>
</table>

Lower in vaccinating areas

Higher in vaccinating areas

Joint SAGE/MPAG session on RTS,S/AS01 Malaria Vaccine
Cerebral malaria

Ghana (MAY2019-APR2021)
Age-eligible cases 4 11
Age-ineligible cases 36 35
Rate ratio . .

Kenya (SEPT2019-APR2021)
Age-eligible cases 13 11
Age-ineligible cases 52 40
Rate ratio . .

Malawi (MAY2019-APR2021)
Age-eligible cases 8 8
Age-ineligible cases 27 51
Rate ratio . .

Pooled (MAY2019-APR2021)
Age-eligible cases 25 30
Age-ineligible cases 115 126
Rate ratio . .

Rate Ratio (95% CI)

0.77 (0.44, 1.35)

0.35 (0.13, 0.98)

0.91 (0.39, 2.10)

1.89 (0.48, 7.45)

Rate Ratio (implementing:comparison)

Lower in vaccinating areas

Higher in vaccinating areas
Mortality among girls compared to boys, all causes except injuries

GIRLS

<table>
<thead>
<tr>
<th>Country</th>
<th>Vaccinated</th>
<th>Comparison</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghana (MAY2019-APR2021)</td>
<td>143</td>
<td>106</td>
<td>0.87 (0.67, 1.14)</td>
</tr>
<tr>
<td>Age-eligible cases</td>
<td>422</td>
<td>278</td>
<td></td>
</tr>
<tr>
<td>Rate ratio</td>
<td>.</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td>Kenya (SEPT2019-APR2021)</td>
<td>356</td>
<td>329</td>
<td>0.92 (0.75, 1.13)</td>
</tr>
<tr>
<td>Age-eligible cases</td>
<td>613</td>
<td>522</td>
<td></td>
</tr>
<tr>
<td>Rate ratio</td>
<td>.</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td>Malawi (MAY2019-APR2021)</td>
<td>561</td>
<td>549</td>
<td>1.06 (0.90, 1.25)</td>
</tr>
<tr>
<td>Age-eligible cases</td>
<td>980</td>
<td>1014</td>
<td></td>
</tr>
<tr>
<td>Rate ratio</td>
<td>.</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td>Pooled (MAY2019-APR2021)</td>
<td>1060</td>
<td>986</td>
<td>0.98 (0.87, 1.09); p = 0.882</td>
</tr>
<tr>
<td>Age-eligible cases</td>
<td>2015</td>
<td>1814</td>
<td></td>
</tr>
<tr>
<td>Rate ratio</td>
<td>.</td>
<td>.</td>
<td></td>
</tr>
</tbody>
</table>

BOYS

<table>
<thead>
<tr>
<th>Country</th>
<th>Vaccinated</th>
<th>Comparison</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>149</td>
<td>124</td>
<td>0.90 (0.65, 1.24)</td>
</tr>
<tr>
<td>Age-eligible cases</td>
<td>451</td>
<td>336</td>
<td></td>
</tr>
<tr>
<td>Rate ratio</td>
<td>.</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>371</td>
<td>341</td>
<td>0.94 (0.75, 1.17)</td>
</tr>
<tr>
<td>Age-eligible cases</td>
<td>696</td>
<td>581</td>
<td></td>
</tr>
<tr>
<td>Rate ratio</td>
<td>.</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>571</td>
<td>678</td>
<td>0.90 (0.74, 1.08)</td>
</tr>
<tr>
<td>Age-eligible cases</td>
<td>1066</td>
<td>1133</td>
<td></td>
</tr>
<tr>
<td>Rate ratio</td>
<td>.</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1061</td>
<td>1143</td>
<td>0.91 (0.80, 1.04); p = 0.153</td>
</tr>
<tr>
<td>Age-eligible cases</td>
<td>2203</td>
<td>2060</td>
<td></td>
</tr>
<tr>
<td>Rate ratio</td>
<td>.</td>
<td>.</td>
<td></td>
</tr>
</tbody>
</table>
Impact on mortality (excluding deaths due to injury) in age groups eligible to have received 3 doses of RTS,S/AS01

<table>
<thead>
<tr>
<th>Country</th>
<th>(Month-Year)</th>
<th>Age-eligible cases</th>
<th>Age-ineligible cases</th>
<th>Rate ratio</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghana</td>
<td>MAY2019-APR2021</td>
<td>151</td>
<td>873</td>
<td></td>
<td>0.85 (0.65, 1.11)</td>
</tr>
<tr>
<td>Kenya</td>
<td>SEPT2019-APR2021</td>
<td>439</td>
<td>1299</td>
<td></td>
<td>0.89 (0.74, 1.07)</td>
</tr>
<tr>
<td>Malawi</td>
<td>MAY2019-APR2021</td>
<td>831</td>
<td>2046</td>
<td></td>
<td>0.97 (0.84, 1.13)</td>
</tr>
<tr>
<td>Pooled</td>
<td>MAY2019-APR2021</td>
<td>1421</td>
<td>4218</td>
<td></td>
<td>0.93 (95% CI 0.84, 1.03)</td>
</tr>
</tbody>
</table>

Rate Ratio (implementing:comparison)

Lower in vaccinating areas

Higher in vaccinating areas
Impact of RTS,S/AS01 introduction in age groups eligible to have received for 3 doses of RTS,S/AS01

Severe malaria

<table>
<thead>
<tr>
<th>Location</th>
<th>Vaccinating</th>
<th>Comparison</th>
<th>Age-eligible cases</th>
<th>Age-ineligible cases</th>
<th>Rate ratio</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghana (MAY2019-APR2021)</td>
<td>51</td>
<td>97</td>
<td>318</td>
<td>302</td>
<td></td>
<td>0.50 (0.25, 1.01)</td>
</tr>
<tr>
<td>Kenya (SEPT2019-APR2021)</td>
<td>132</td>
<td>106</td>
<td>427</td>
<td>309</td>
<td></td>
<td>0.90 (0.56, 1.46)</td>
</tr>
<tr>
<td>Malawi (MAY2019-APR2021)</td>
<td>235</td>
<td>486</td>
<td>568</td>
<td>779</td>
<td></td>
<td>0.66 (0.45, 0.99)</td>
</tr>
<tr>
<td>Pooled (MAY2019-APR2021)</td>
<td>418</td>
<td>689</td>
<td>1313</td>
<td>1390</td>
<td></td>
<td><strong>0.70 (95% CI 0.54, 0.92)</strong></td>
</tr>
</tbody>
</table>

Rate Ratio (implementing:comparison)

Lower in vaccinating areas ↔ Higher in vaccinating areas
Survey estimates of coverage of the first dose of RTS,S/AS01 in children 12-23 months of age, in implementation and comparison areas

<table>
<thead>
<tr>
<th>Eligible age groups</th>
<th>Older age groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Implementation areas</td>
</tr>
<tr>
<td>HBR recall</td>
<td>HBR recall</td>
</tr>
<tr>
<td>Malawi</td>
<td>0.741 0.555</td>
</tr>
<tr>
<td>Ghana</td>
<td>0.797 0.248</td>
</tr>
<tr>
<td>Kenya</td>
<td>0.795 0.72</td>
</tr>
</tbody>
</table>

(Older age groups not surveyed in Kenya)
Association of RTS,S/AS01 introduction with the incidence of cerebral malaria in age-groups of children eligible to have received RTS,S

Cases with *P. falciparum* infection, with impaired consciousness, in whom LP was performed to exclude meningitis:

There were 296 such cases of cerebral malaria, out of a total of 4331 cases of severe malaria in sentinel hospitals:

<table>
<thead>
<tr>
<th></th>
<th>Cases in eligible age groups</th>
<th>Cases in non-eligible age groups</th>
<th>Incidence rate ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>296 cases of cerebral malaria (LP performed to exclude meningitis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparison areas</td>
<td>30</td>
<td>126</td>
<td>1</td>
</tr>
<tr>
<td>RTS,S/AS01 areas</td>
<td>25</td>
<td>115</td>
<td>0.77 (0.44, 1.35)</td>
</tr>
</tbody>
</table>

There was therefore no evidence that introduction of the malaria vaccine led to an increase in the incidence of hospital admission with cerebral malaria.

56% (14/25) of the cases in eligible age groups from implementing areas had received RTS,S/AS01 vaccine compared to 55% of all other admissions in the same age group, consistent with no association of the vaccine with cerebral malaria.
Association of RTS,S/AS01 introduction with the incidence of *cerebral malaria* in age-groups of children eligible to have received RTS,S

*Cases with *P. falciparum* infection, with impaired consciousness, in whom LP was performed to exclude meningitis:*

Results were similar when alternative case definitions of cerebral malaria were used:

<table>
<thead>
<tr>
<th>Cases in eligible age groups</th>
<th>Cases in non-eligible age groups</th>
<th>Incidence rate ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>296 cases of cerebral malaria (LP performed to exclude meningitis)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparison areas</td>
<td>30</td>
<td>126</td>
</tr>
<tr>
<td>RTS,S/AS01 areas</td>
<td>25</td>
<td>115</td>
</tr>
<tr>
<td><strong>558 cases of cerebral malaria (without requirement of LP):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparison areas</td>
<td>54</td>
<td>225</td>
</tr>
<tr>
<td>RTS,S/AS01 areas</td>
<td>49</td>
<td>230</td>
</tr>
<tr>
<td><strong>263 cases of cerebral malaria (Unresponsive on AVPU score):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparison areas</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>RTS,S/AS01 areas</td>
<td>20</td>
<td>118</td>
</tr>
</tbody>
</table>
Association of RTS,S/AS01 introduction with the incidence of meningitis (probable or confirmed) in age-groups of children eligible to have received RTS,S

130 cases of probable or confirmed meningitis in sentinel hospitals:

<table>
<thead>
<tr>
<th></th>
<th>Cases in eligible age groups</th>
<th>Cases in non-eligible age groups</th>
<th>Incidence rate ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison areas</td>
<td>24</td>
<td>35</td>
<td>1</td>
</tr>
<tr>
<td>RTS,S/AS01 areas</td>
<td>27</td>
<td>44</td>
<td>0.81 (0.43,1.55)</td>
</tr>
</tbody>
</table>

There was therefore no evidence that introduction of the malaria vaccine led to an increase in the incidence of hospital admission with meningitis.

40.7% (11/27) of the cases in eligible age groups from implementing areas had received RTS,S/AS01 vaccine compared to 53% of all other admissions in the same age group, consistent with no association of the vaccine with meningitis.
Association of RTS,S/AS01 introduction with **mortality of any cause except injury**, in children eligible for (at least 1 dose of) RTS,S/AS01

<table>
<thead>
<tr>
<th>Both sexes</th>
<th>Deaths in eligible age groups</th>
<th>Deaths in non-eligible age groups</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison areas</td>
<td>2129</td>
<td>3874</td>
<td>1</td>
</tr>
<tr>
<td>RTS,S/AS01 areas</td>
<td>2151</td>
<td>4218</td>
<td>0.94 (0.85,1.03)</td>
</tr>
</tbody>
</table>
Association of RTS,S/AS01 introduction with mortality of any cause except injury, in children eligible for (at least 1 dose of) RTS,S/AS01

<table>
<thead>
<tr>
<th>Both sexes</th>
<th>deaths in eligible age groups</th>
<th>deaths in non-eligible age groups</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison areas</td>
<td>2129</td>
<td>3874</td>
<td>1</td>
</tr>
<tr>
<td>RTS,S/AS01 areas</td>
<td>2151</td>
<td>4218</td>
<td>0.94 (0.85,1.03)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Girls</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison areas</td>
<td>986</td>
<td>1814</td>
<td>1</td>
</tr>
<tr>
<td>RTS,S/AS01 areas</td>
<td>1060</td>
<td>2015</td>
<td>0.98 (0.87,1.09)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Boys</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison areas</td>
<td>1143</td>
<td>2060</td>
<td>1</td>
</tr>
<tr>
<td>RTS,S/AS01 areas</td>
<td>1091</td>
<td>2203</td>
<td>0.91 (0.80,1.04)</td>
</tr>
</tbody>
</table>

Ratio of the mortality rate ratios (girls:boys): 1.08 (0.93, 1.25)
P-value for difference between girls and boys p=0.321

No evidence the impact of RTS,S/AS01 introduction on mortality differs between girls and boys, in these age groups
Percentage of deaths in vaccinating areas, in age groups eligible to have received RTS,S/AS01, who had received the vaccine*, among girls and among boys

<table>
<thead>
<tr>
<th>Girls from implementing areas (age groups eligible to have received RTS,S/AS01)</th>
<th>Boys from implementing areas (age groups eligible to have received RTS,S/AS01)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% received RTS,S/AS01</td>
<td>58.9% (495/841)</td>
</tr>
</tbody>
</table>

*From Home-Based Record or caregiver recall, collected during Vas, with reliance on recall: Home-Based Record available for 79% Ghana; 48% Kenya; 12% Malawi for facility deaths, 29% for community deaths. Coverage of RTS,S is slightly higher in girls compared to boys in the midline household surveys in Ghana and Malawi, similar in Kenya.

Data on vaccination status are consistent with no difference between girls and boys in the impact of RTS,S/AS01 on all-cause mortality: 58.9% of girls,
Association of RTS,S/AS01 introduction with mortality of any cause except injury, in children eligible for (at least 1 dose of) RTS,S/AS01

Sub-analysis in older eligible children (18+ months)

<table>
<thead>
<tr>
<th></th>
<th>Girls deaths in eligible age groups 18+ months old</th>
<th>girls deaths in non-eligible age groups</th>
<th>Mortality rate ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison areas</td>
<td>163</td>
<td>1814</td>
<td>1</td>
</tr>
<tr>
<td>RTS,S/AS01 areas</td>
<td>157</td>
<td>2015</td>
<td>0.91 (0.73,1.12)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Boys deaths in eligible age groups 18+ months old</th>
<th>Boys deaths in non-eligible age groups</th>
<th>Mortality rate ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison areas</td>
<td>181</td>
<td>2060</td>
<td>1</td>
</tr>
<tr>
<td>RTS,S/AS01 areas</td>
<td>180</td>
<td>2203</td>
<td>0.94 (0.76,1.17)</td>
</tr>
</tbody>
</table>

Ratio of the mortality rate ratios (girls:boys): 0.95 (0.70, 1.31)
P-value for difference between girls and boys p=0.770

No evidence the impact of RTS,S/AS01 introduction on mortality differs between girls and boys, in children 18-30 months
### Comparison of signals observed in the phase 3 trial, with associations observed in the MVIP

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rate ratio in the phase 3 trial (95%CI)*</th>
<th>Rate ratio of the phase 3 trial, adjusted for MVIP coverage** (95%CI)</th>
<th>Rate ratio in the MVIP (95%CI)</th>
<th>p-value for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>10.5 (1.4, 78)</td>
<td>3.92 (1.22, 12.6)</td>
<td>0.81 (0.43, 1.55)</td>
<td>0.0207</td>
</tr>
<tr>
<td>Cerebral malaria</td>
<td>2.15 (1.1, 4.3)</td>
<td>1.60 (1.05, 2.43)</td>
<td>0.77 (0.44, 1.35)</td>
<td>0.0397</td>
</tr>
<tr>
<td>Relative mortality ratio between girls and boys</td>
<td>2.6 (1.29, 5.26)</td>
<td>1.83 (1.17, 2.85)</td>
<td>1.08 (0.93, 1.25)</td>
<td>0.0285</td>
</tr>
</tbody>
</table>

* R3R and R3C combined compared to C3C, ITT to study end

** Allowing for vaccine uptake in implementation areas, and effects of contamination, that would dilute the effects if they occurred in the MVIP

The hypothesis that the safety signal observed in the phase 3 trial occurred in the pilot implementations of RTS,S/AS01 was rejected, for each of the three signals.
Rate ratios for safety endpoints among children eligible to have received 1+ vaccine doses

<table>
<thead>
<tr>
<th></th>
<th>Rate ratio* (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality excluding accidents and trauma by gender:</td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>0.98 (0.87, 1.09)</td>
</tr>
<tr>
<td>Boys</td>
<td>0.91 (0.80, 1.04)</td>
</tr>
<tr>
<td>Interaction</td>
<td>1.08 (0.93, 1.25); p = 0.32</td>
</tr>
<tr>
<td>Probable or confirmed meningitis</td>
<td>0.81 (0.43, 1.55)</td>
</tr>
<tr>
<td>Cerebral malaria (a subset of severe malaria)</td>
<td>0.77 (0.44, 1.35)</td>
</tr>
<tr>
<td>Interaction vs other severe malaria</td>
<td>0.94 (0.57, 1.56); p = 0.81</td>
</tr>
</tbody>
</table>

*percentage reduction in incidence associated with introduction of the RTS,S/AS01 vaccine, among the age group of children eligible to have received at least 1 dose of the vaccine.
Malaria vaccination delivery options (illustrative)

Perennial transmission settings
Year-around Delivery
4 doses through the routine EPI

Seasonal Delivery Option 1
Initial 3 doses in routine EPI then annual doses before high transmission season

Seasonal Delivery Option 2
Initial 3 doses and subsequent annual doses just prior to the high transmission season

*Assumption that a country chooses schedule 5, 6, 7 months of age for dose 1, 2, 3, respectively.