Overview of the Malaria Vaccine Implementation Programme (MVIP)

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SAGE meeting

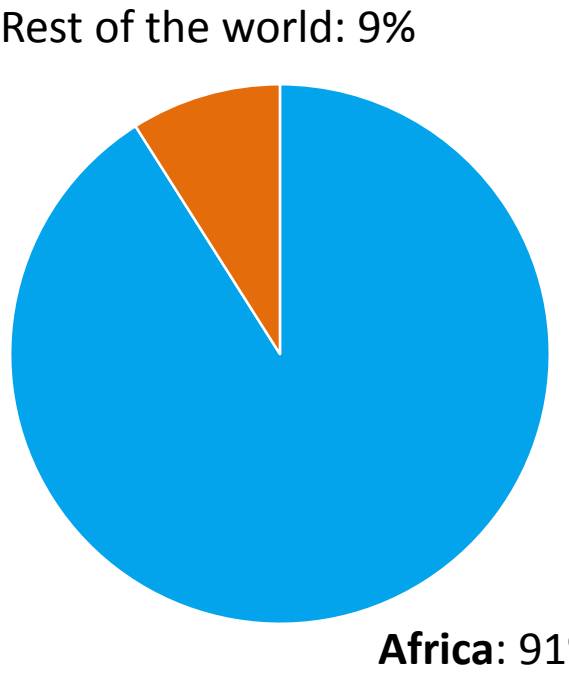
17 April, 2018

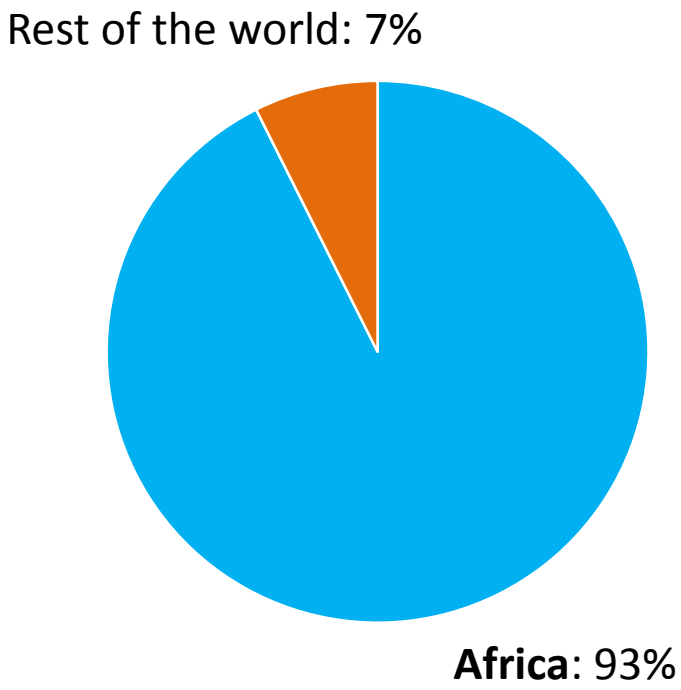
Objectives

- Brief review
  - Background
  - EMA positive opinion and WHO recommendations
- Funding
- Description of the Malaria Vaccine Implementation Programme (MVIP)
- Governance structure

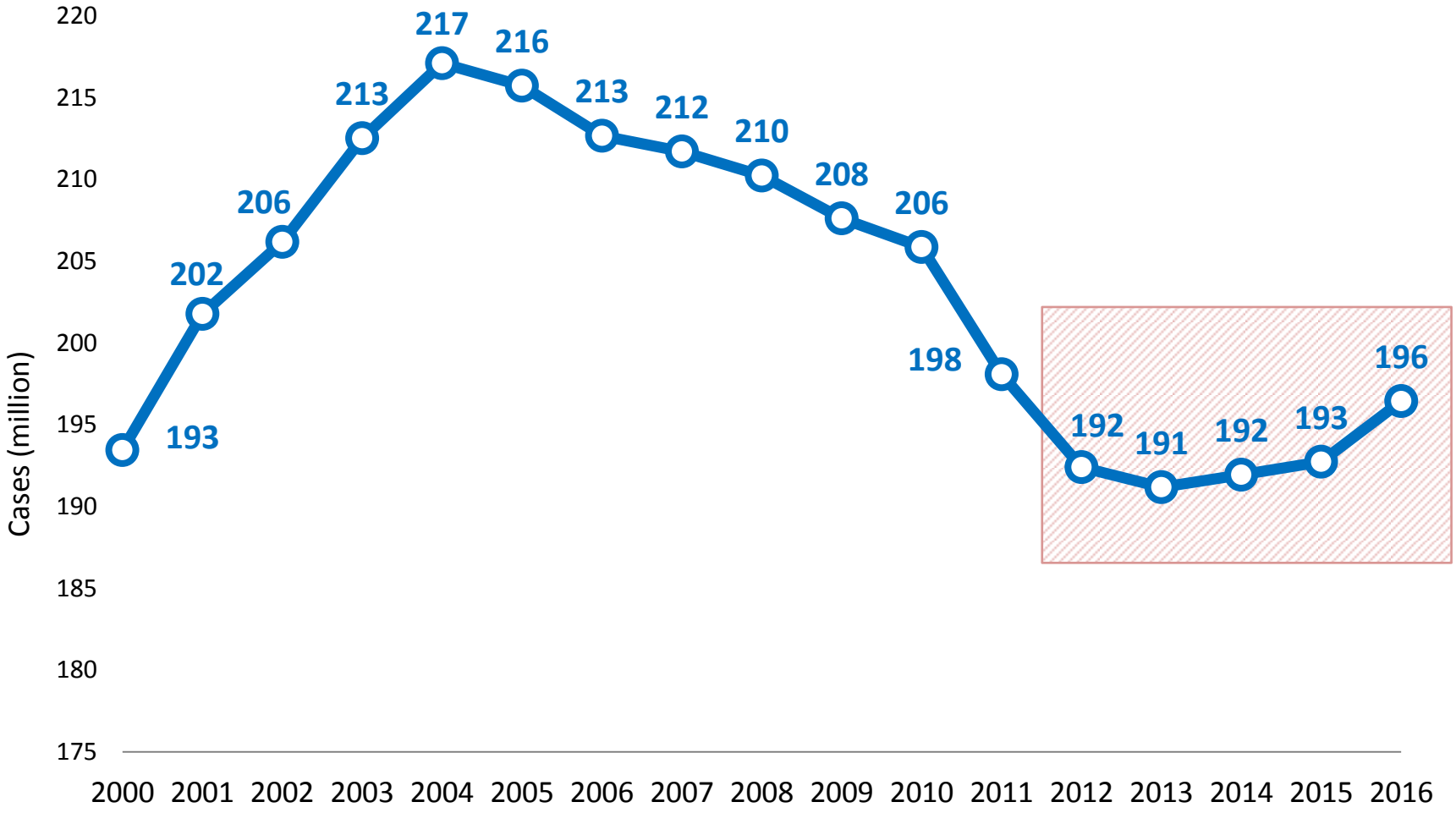
Estimated malaria cases & deaths in the World and relative contribution of the African region, 2016

Cases 216 million **Deaths 445 thousand**

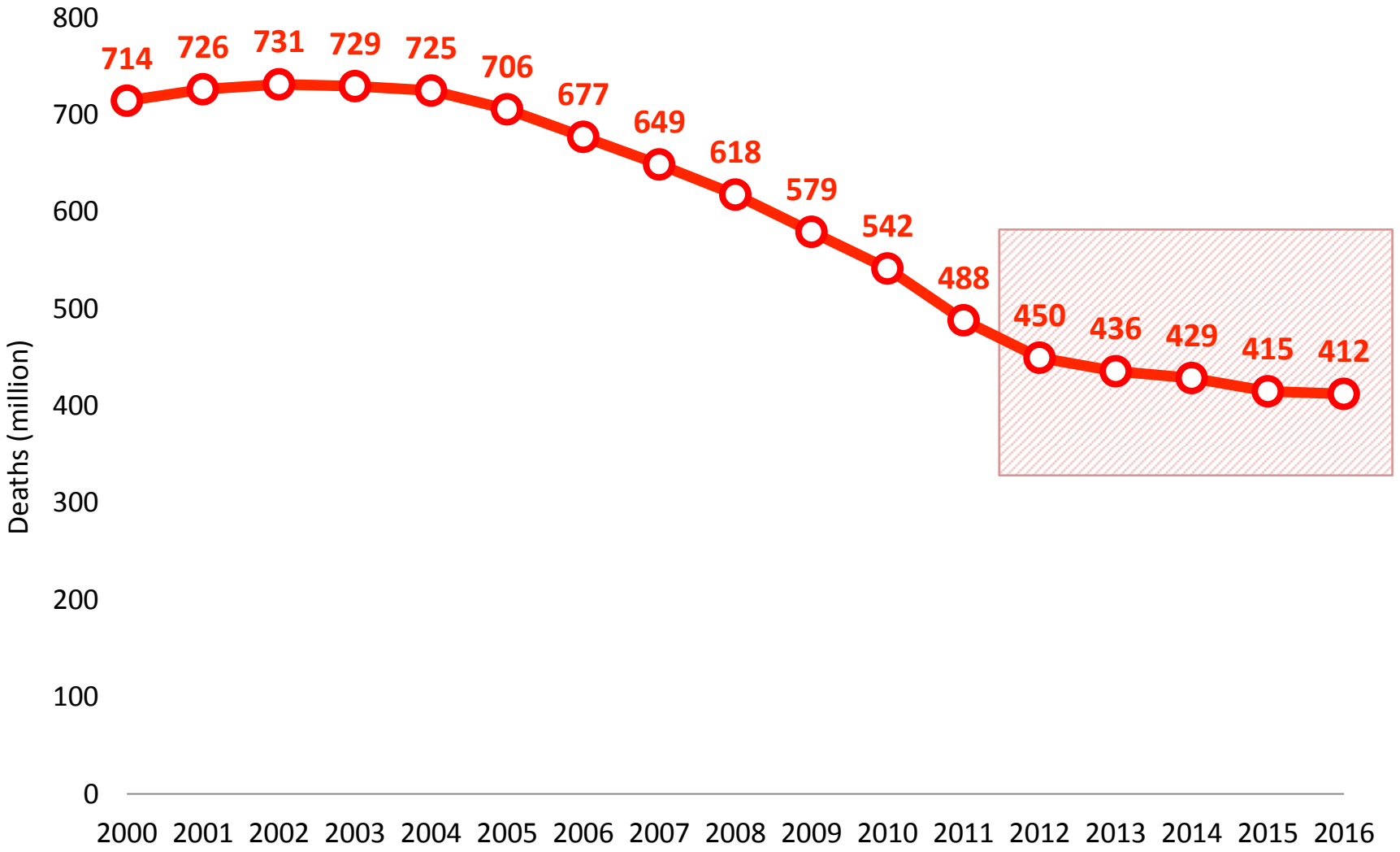




Number of malaria cases in the African Region, 2000-2016

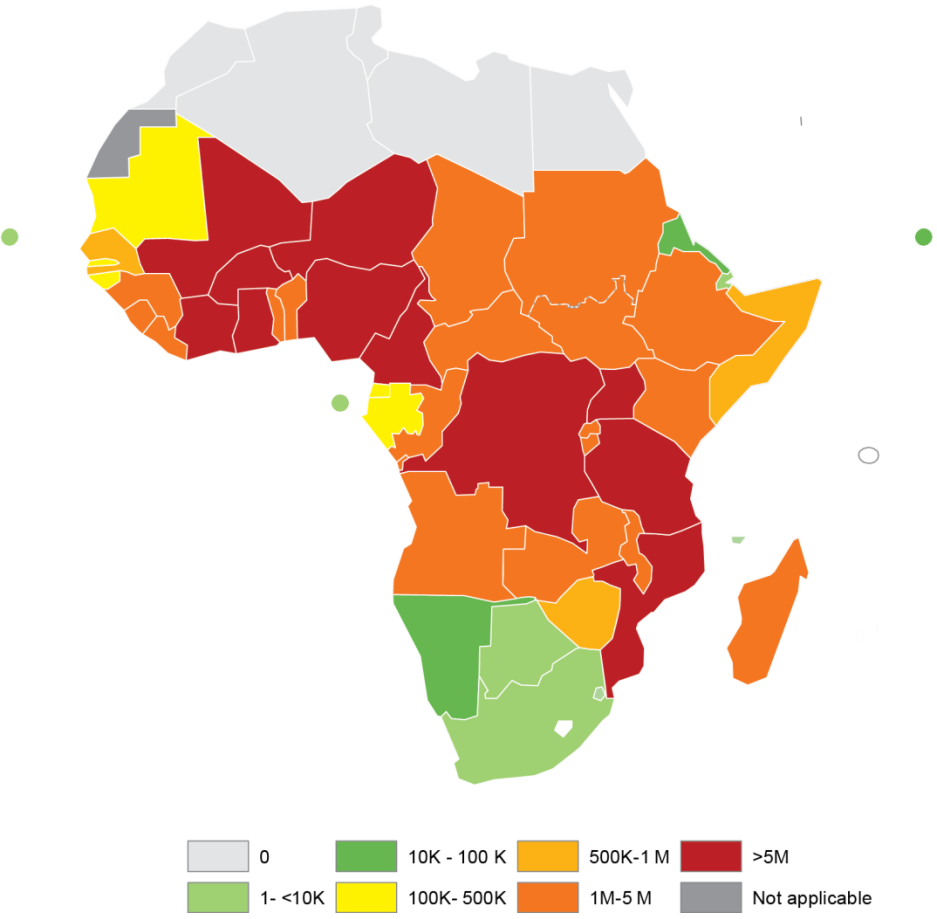


Number of malaria deaths in the African Region, 2000-2016

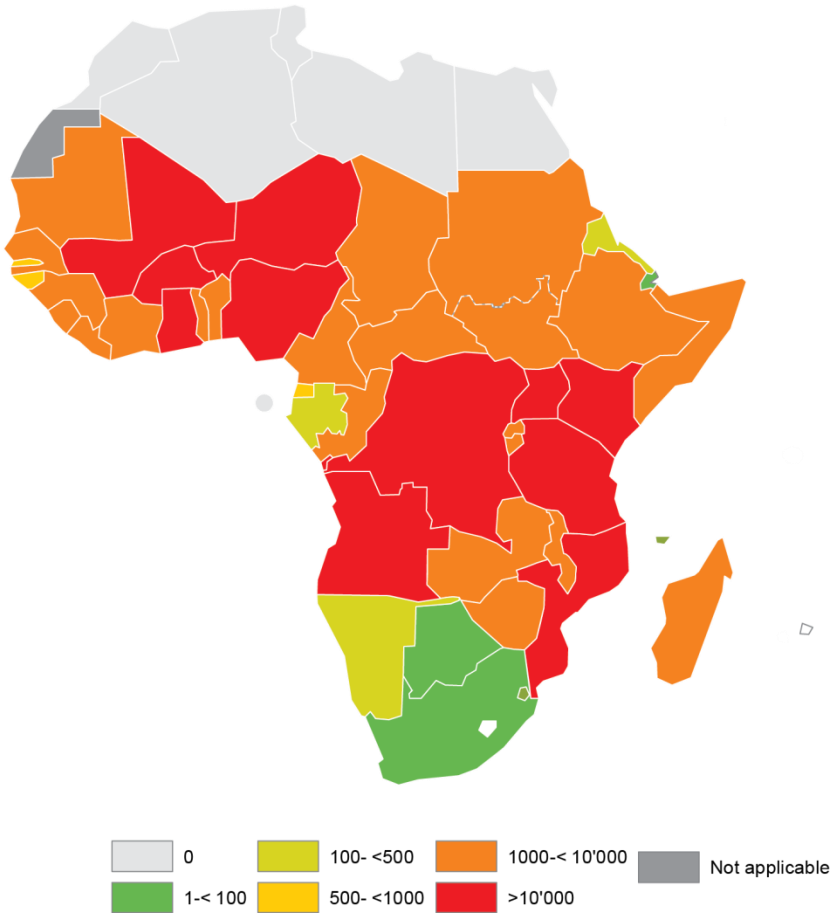


Malaria cases and deaths, 2016

Cases



Deaths



KEY RESULTS FROM PHASE 3 TRIAL OF RTS,S/AS01 IN 11 SITES IN 7 AFRICAN COUNTRIES: CHILDREN 5-17 MONTHS OF AGE AT FIRST VACCINATION

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% (34-43)
Severe malaria	32% (9.3-48)
Incident severe malaria anaemia	61% (26.5-81)
Blood transfusion	29%, (3.5-47)
Malaria hospitalization	37% (23.6-49)

Primary manifestation of severe malaria in high transmission settings

*Efficacy against severe disease lost without 4th dose. Median follow-up period 48 months.
** Trial not designed to show VE on mortality. Very low mortality among study participants. At Siaya site, case control analysis showed enrolled children had 70% decreased risk of mortality

Safety Signal

Related

- Increased risk of febrile convulsions within 7 days of vaccination

Relationship to vaccine not established

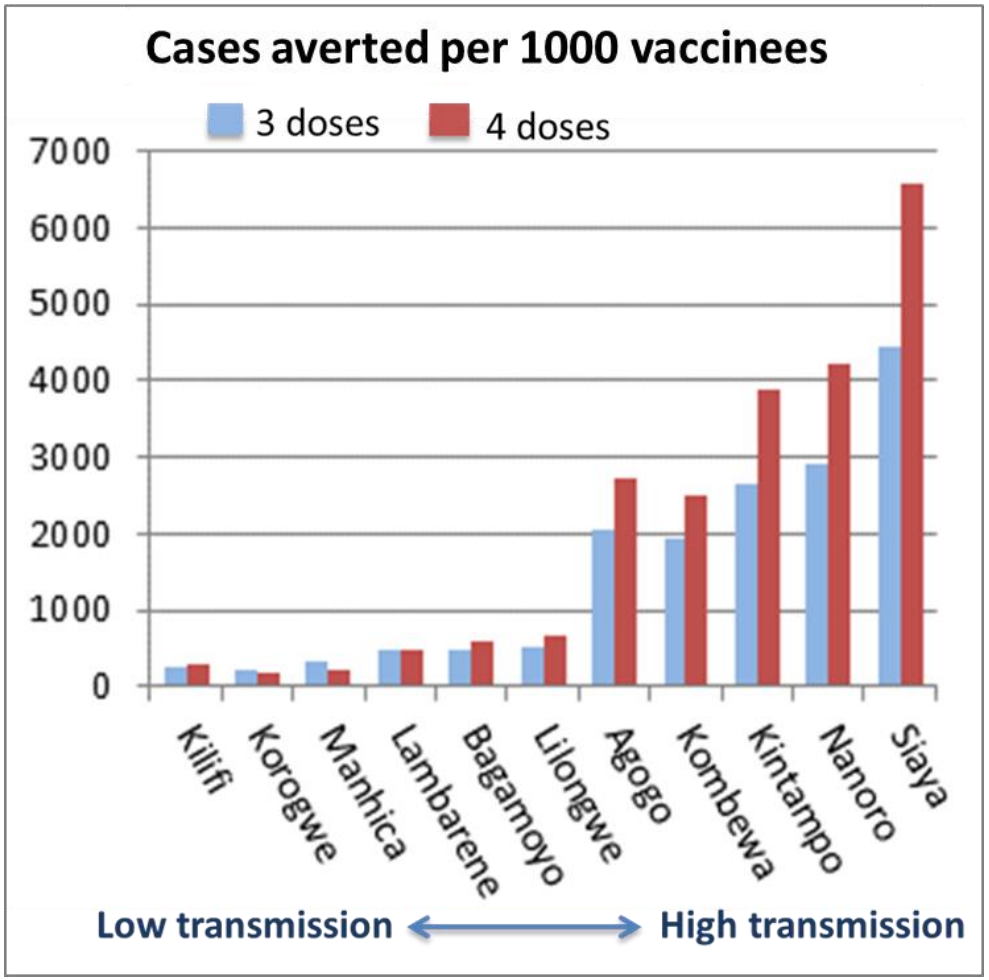
- Increased risk of meningitis
- Increased risk of cases of cerebral malaria
- Among low number of children who died, girls vaccinated with RTS,S vaccine were more likely to die than girls vaccinated with comparator vaccines
  - No vaccine-related deaths

VACCINE IMPACT

Vaccine Impact Observed in Phase III Trial

Cases of clinical malaria averted per 1000 vaccines in 5-17 month age group (ITT , [0-SE])

- While efficacy is modest, the number of episodes of malaria averted in high transmission settings is substantial
  - Impact with 4 doses in high transmission areas: several thousand per 1000 children vaccinated over 4 yrs follow-up
- Focus of pilots will be in such high transmission settings



 Lancet, RTS,S Clinical Trials partnership, 2015

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Summary of Modelled Impact

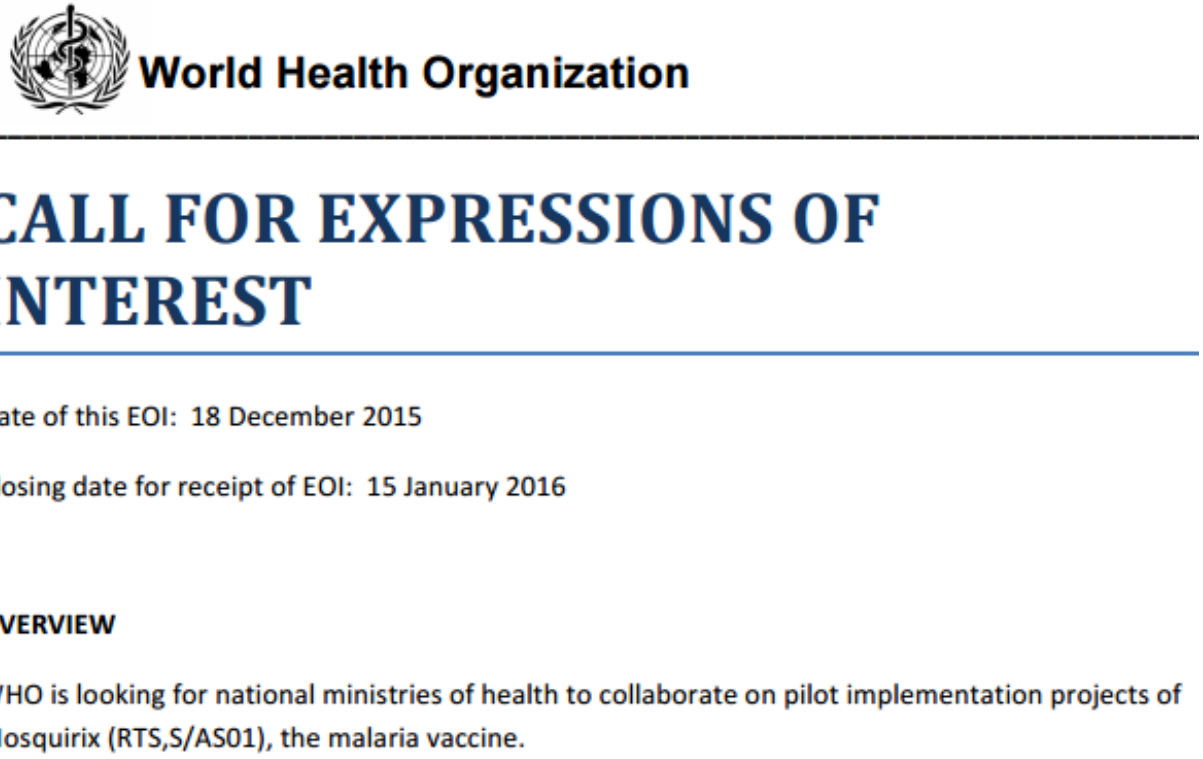
- WHO oversaw a modelling exercise from 4 groups (Imperial College, Swiss TPH, Intellectual Ventures, GSK), leading to consensus estimates for impact and cost-effectiveness
- All models predict an overall beneficial impact of the vaccine on mortality
- **Consensus range is 10% to 28% reduction for under 5 year olds, in malaria-related deaths among fully vaccinated children**

EUROPEAN MEDICINES AGENCY OPINION & WHO RECOMMENDATION

EMA Article 58: Positive Scientific Opinion and WHO Recommendation

- EMA has issued a **positive scientific opinion**,
  - Stating that the safety profile is “acceptable” and risk-benefit profile “favourable” from a regulatory perspective, applying the same rigorous standards as for medicines to be marketed in the EU
- WHO recognized potential for vaccine’s high impact and recommends phased introduction in pilot implementations to answer outstanding key questions in routine setting on
  - Feasibility
  - Safety
  - Impact

Country-selection: Public Call for Expression of Interest



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CALL FOR EXPRESSIONS OF INTEREST

Date of this EOI: 18 December 2015

Closing date for receipt of EOI: 15 January 2016

OVERVIEW

WHO is looking for national ministries of health to collaborate on pilot implementation projects of Mosquirix (RTS,S/AS01), the malaria vaccine.

- **10 countries expressed interest**
- **Kenya, Ghana, Malawi selected using standardized criteria**

Funding

- $49.2 million in funding commitments for MVIP Phase 1 (2017-2020) secured from:
  - Gavi, the Vaccine Alliance: $24.6 million
  - Global Fund to Fight AIDS, Tuberculosis and Malaria: $15 million
  - Unitaid: $9.6 million

- Vaccine for MVIP donated by GSK (up to 10 million doses)

MALARIA VACCINE PILOT IMPLEMENTATIONS

WHO recommended a pilot implementation programme involving:

1. **Sub-national introduction of the RTS,S malaria vaccine:**
   - Vaccine only will be used after authorized for use in the pilots
   - **Country EPI Programme-led** new vaccine introduction, with RTS,S delivered by the EPI programme using existing mechanisms
   - Emphasis on maintaining a real world introduction

2. **Rigorous evaluation, supported by research institutions, to measure**:
   - **Operational feasibility** of providing RTS,S at the recommended four-dose schedule when implemented through the routine EPI;
   - Frequency of **adverse events** following immunisation (AEFI), with an emphasis on **meningitis** and **cerebral malaria;**
   - **Impact** of the vaccine on all cause child mortality (overall and by gender), malaria-specific mortality and severe malaria;

In Addition, the MVIP includes

3. **GSK-led** phase IV observational study on safety, effectiveness and impact in routine use with both active and enhanced hospital surveillance – part of RTS,S/AS01 Risk Management Plan between GSK and EMA to further assess vaccine.

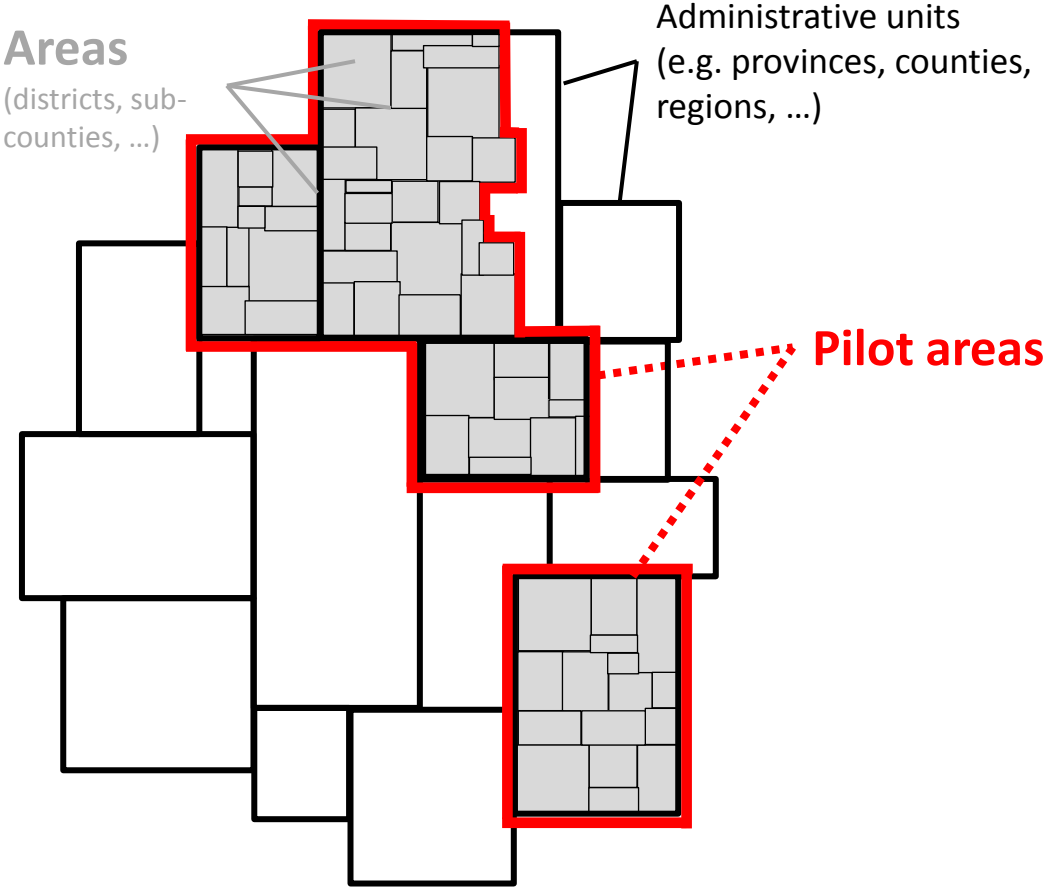
4. **PATH-led qualitative assessment** to explore and document any changes in health seeking strategies and the health service provision of the RTS,S malaria vaccine; and **economic analyses**

Vaccine introduction

- Sub-national introduction of RTS,S enables some areas to introduce RTS,S at the beginning of the programme, while other areas act as a comparison
  - Allocation of areas to implementation or comparison will be randomized
  - Areas defined based on country context and evaluation requirements (e.g. district in Ghana; sub-county in Kenya; clusters in Malawi)

Illustration of randomized vaccine introduction

Hypothetical Country



1. Identification of pilot area and units for randomized introduction

2. Set up of standardized monitoring systems in all areas to monitor safety and survival

3. Randomization of areas

   - Implement RTS,S
   - Comparison areas

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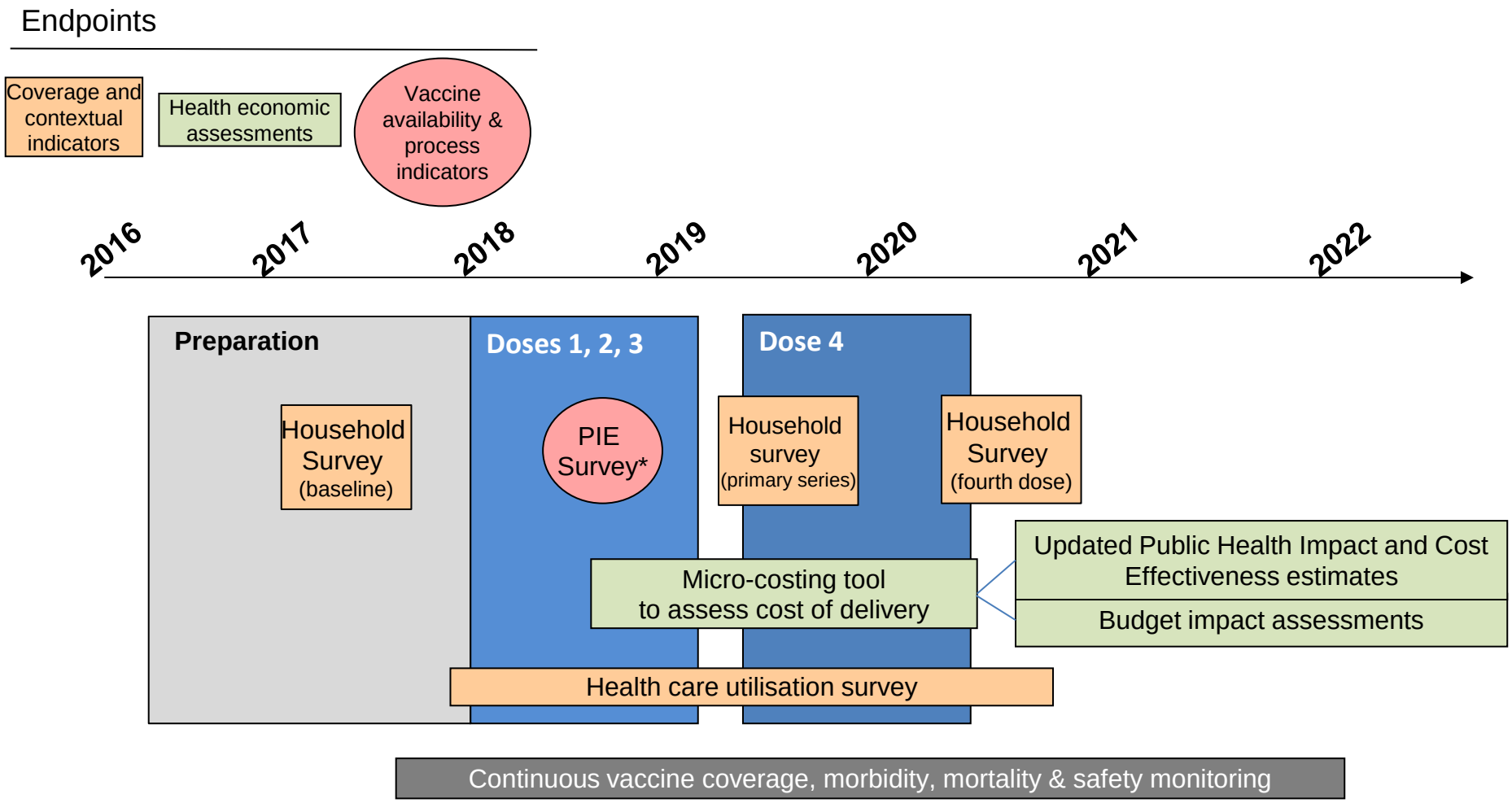
Feasibility evaluation components

Approximate timings in 1 country. Countries are likely to start pilot implementation activities within 6 months of each other



*New Vaccine Post-Introduction Evaluation

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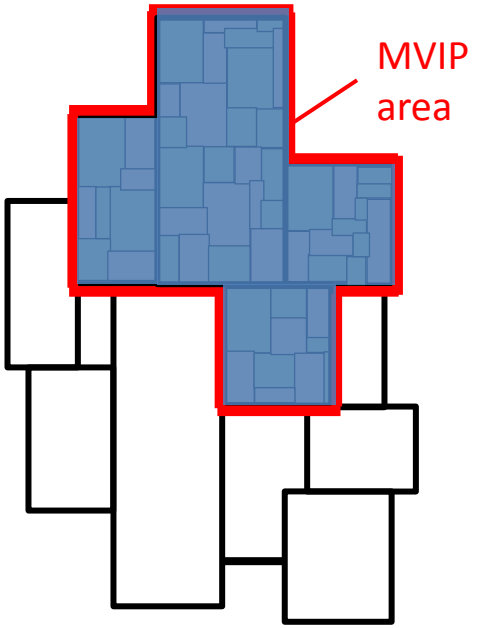
MVIP Safety Evaluation for RTS,S

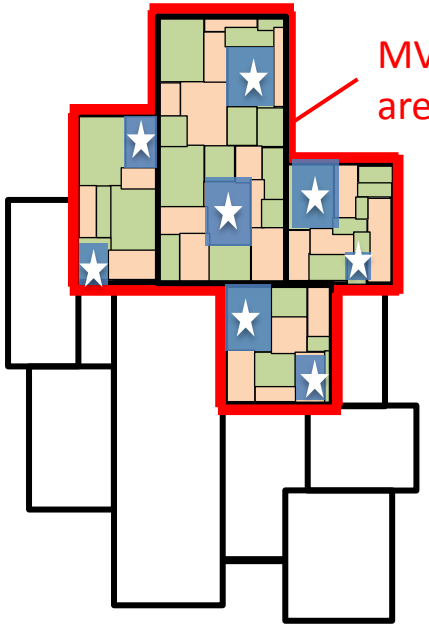
Pharmacovigilance: routine spontaneous AEFI/AESI reporting
Focus on rare/unexpected events

Mortality surveillance



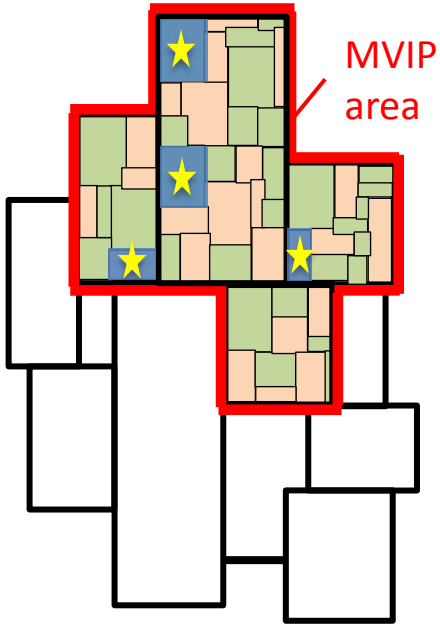
All areas

In-patient surveillance at sentinel hospitals
Focus on meningitis and cerebral malaria, hospitalized AEFI/AESIs



Approximately
8 sentinel hospitals*

GSK Phase IV in-patient surveillance/home visits
Focus on meningitis, cerebral malaria and AEFI/AESIs



4 sentinel hospitals
+ home visits in 4-6 clusters*

*in each pilot country

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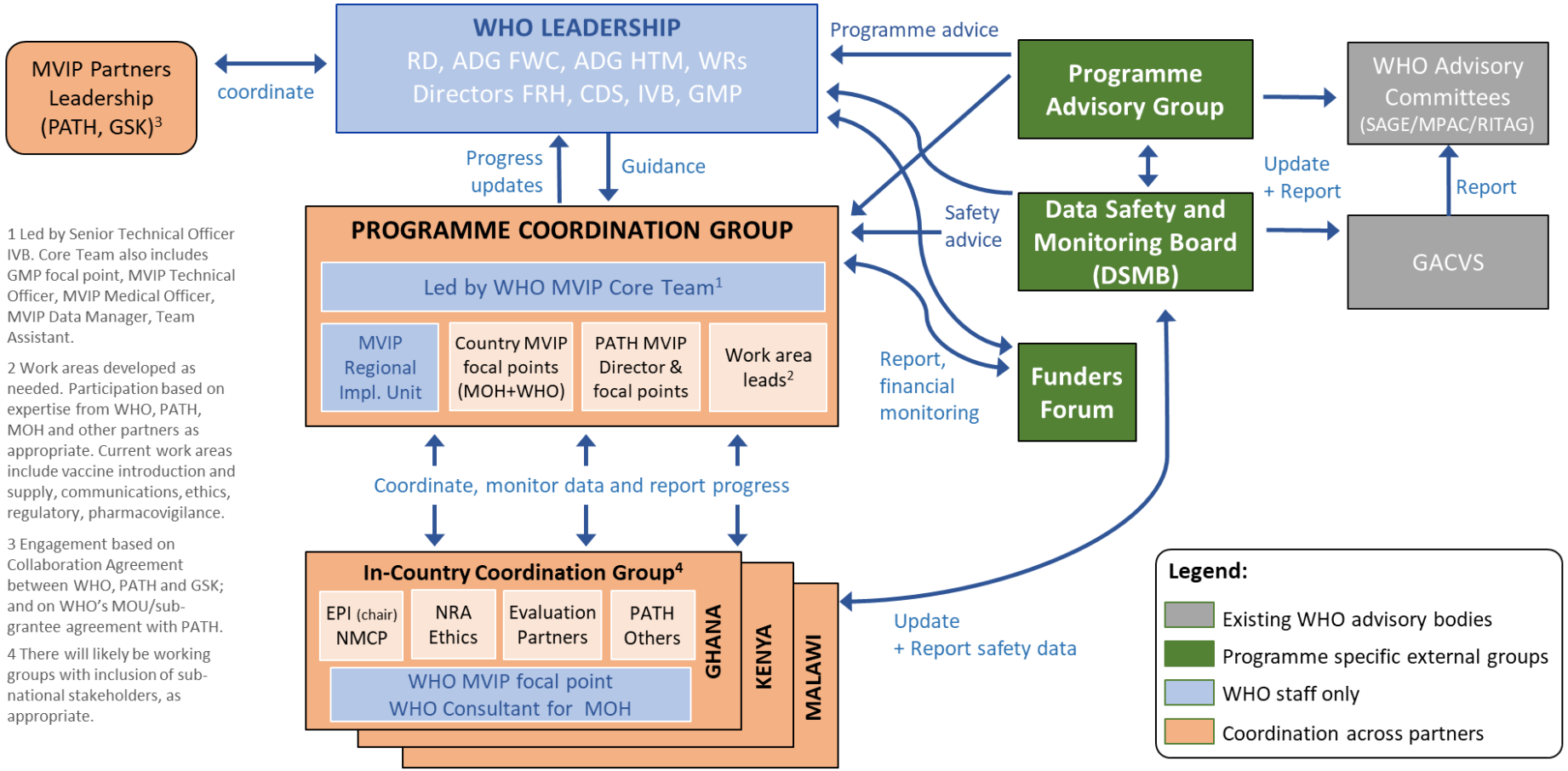
Impact

- Assess the impact of the RTS,S vaccine on:
  - all cause child mortality
    - Community based surveillance relying on village reporters (and verbal autopsies)
  - malaria-specific mortality
    - In patient surveillance
  - severe malaria
    - In patient surveillance

MVIP governance and coordination



1 Led by Senior Technical Officer IVB. Core Team also includes GMP focal point, MVIP Technical Officer, MVIP Medical Officer, MVIP Data Manager, Team Assistant.

2 Work areas developed as needed. Participation based on expertise from WHO, PATH, MOH and other partners as appropriate. Current work areas include vaccine introduction and supply, communications, ethics, regulatory, pharmacovigilance.

3 Engagement based on Collaboration Agreement between WHO, PATH and GSK; and on WHO's MOU/sub-grantee agreement with PATH.

4 There will likely be working groups with inclusion of sub-national stakeholders, as appropriate.

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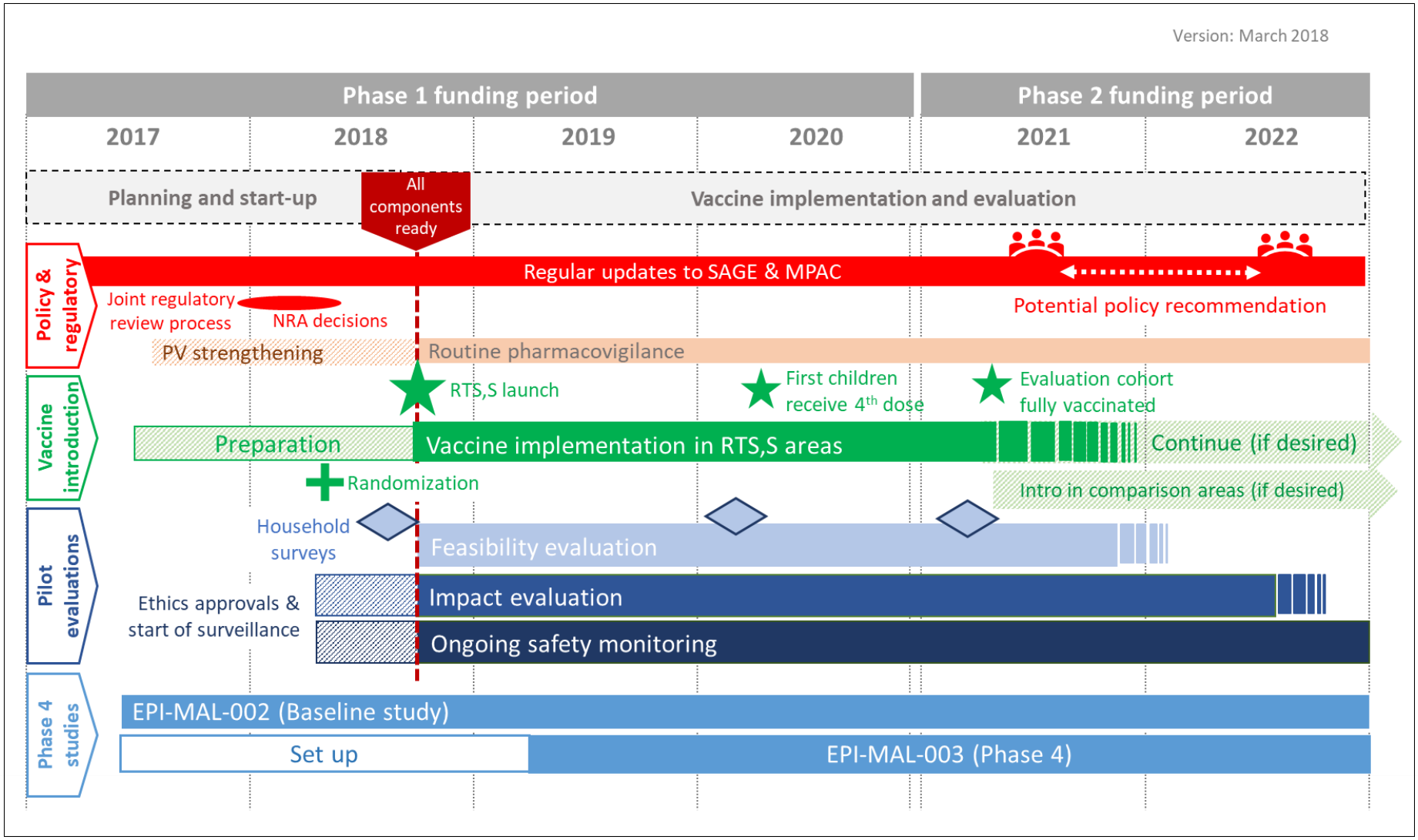
Thank you

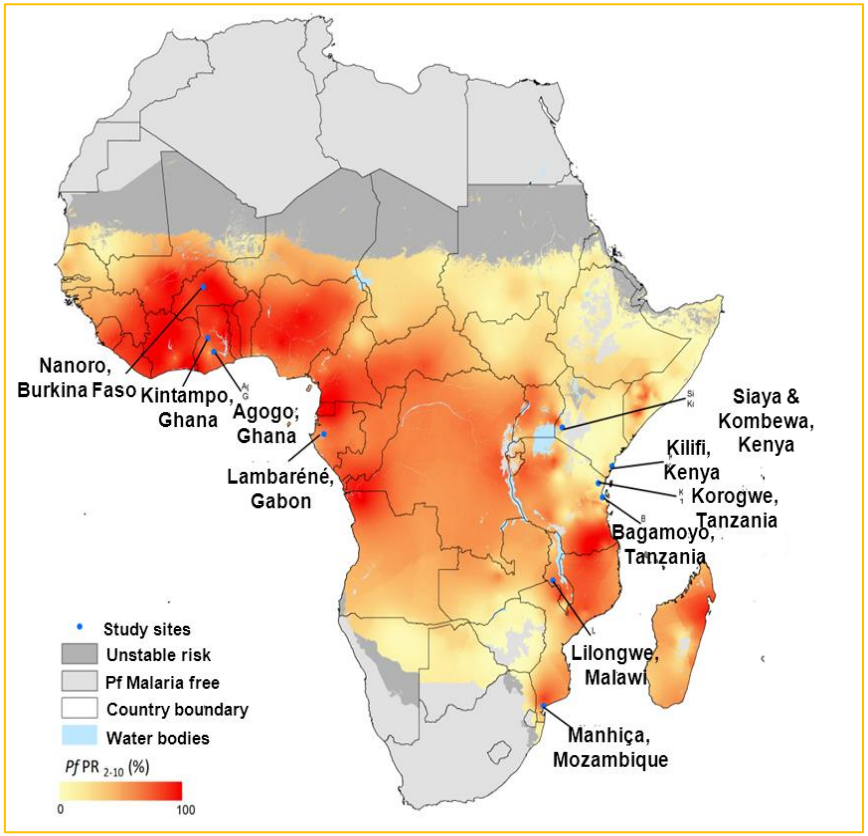
Extra slides

MVIP timeline



Pivotal Phase III RTS,S/AS01 Trial

- Double-blind, individually-randomised, controlled trial of VE, safety, immunogenicity (2009-2014)
- 11 sites in 7 countries: Burkina Faso, Gabon, Ghana (Kumasi, Kintampo), Kenya (Kilifi, Kombewa, Siaya), Malawi (Lilongwe), Mozambique and Tanzania
- Wide range of malaria transmission intensities
- Vaccine given in 4 dose or 3 dose schedule
  - Months 0, 1, 2, 20
- 15,459 children enrolled in two age categories
  - 5 to 17 months
  - 6 to 12 weeks co-administered with EPI
    - VE against severe disease in 6-12 week NS



Leach A., et al. Malaria J 2011; 10:224 ; PLoS Medicine 2014; 11(7): e1001685; Hay SI, Guerra CA, Gething PW et al. A World Malaria Map: Plasmodium falciparum Endemicity in 2007. PLOS Med 2009;6:e1000048

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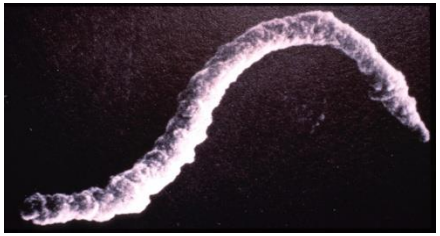
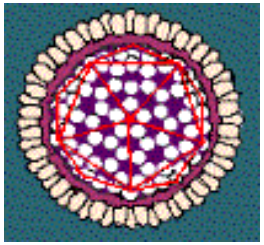
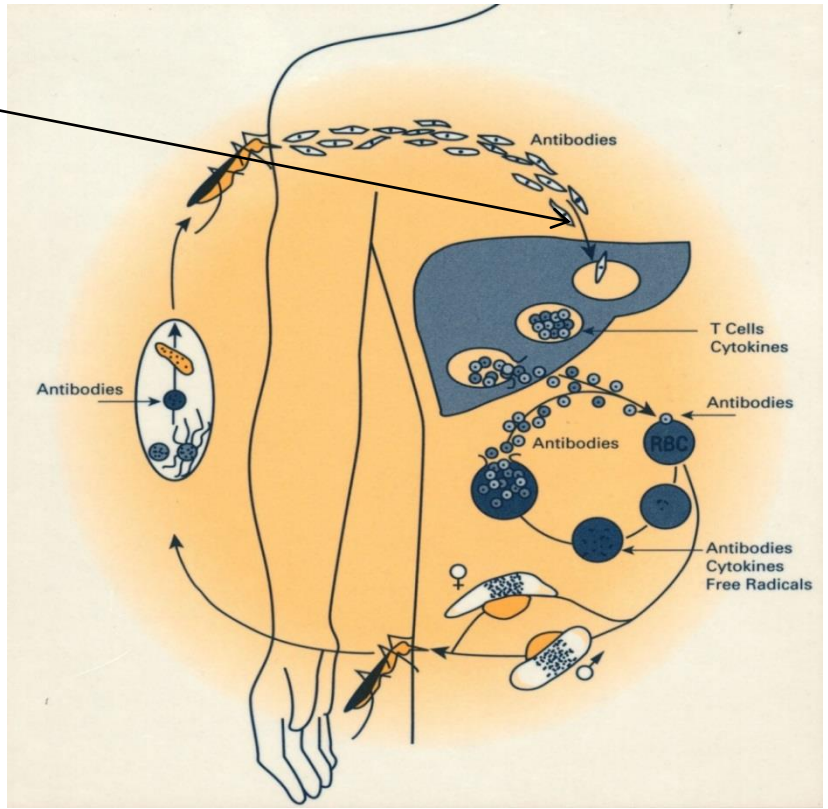
RTS,S/AS01 Vaccine

- RTS,S/AS01 vaccine







  - Combines CS protein, hepatitis B surface antigen, and AS01 adjuvant to create a more robust immune response than nature
  - Vaccine targets the CS protein on the sporozoite of *P. falciparum*

Models indicate RTS,S is cost-effectiveness

- At **a hypothetical** vaccine price of $5 a dose, the median incremental vaccine cost effectiveness ratio is
  - **$87 (range $48-$244) per DALY averted**
  - **$25 ($16-$222) per clinical case averted**
- **RTS,S compares favourably relative to global cost effectiveness estimates of several other vaccines.**

Penny MA et al. Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. 2015, Lancet, Vol. 15, pp. 0140-6736

Summary of Modelled Health Impact Using Mathematical Modelling

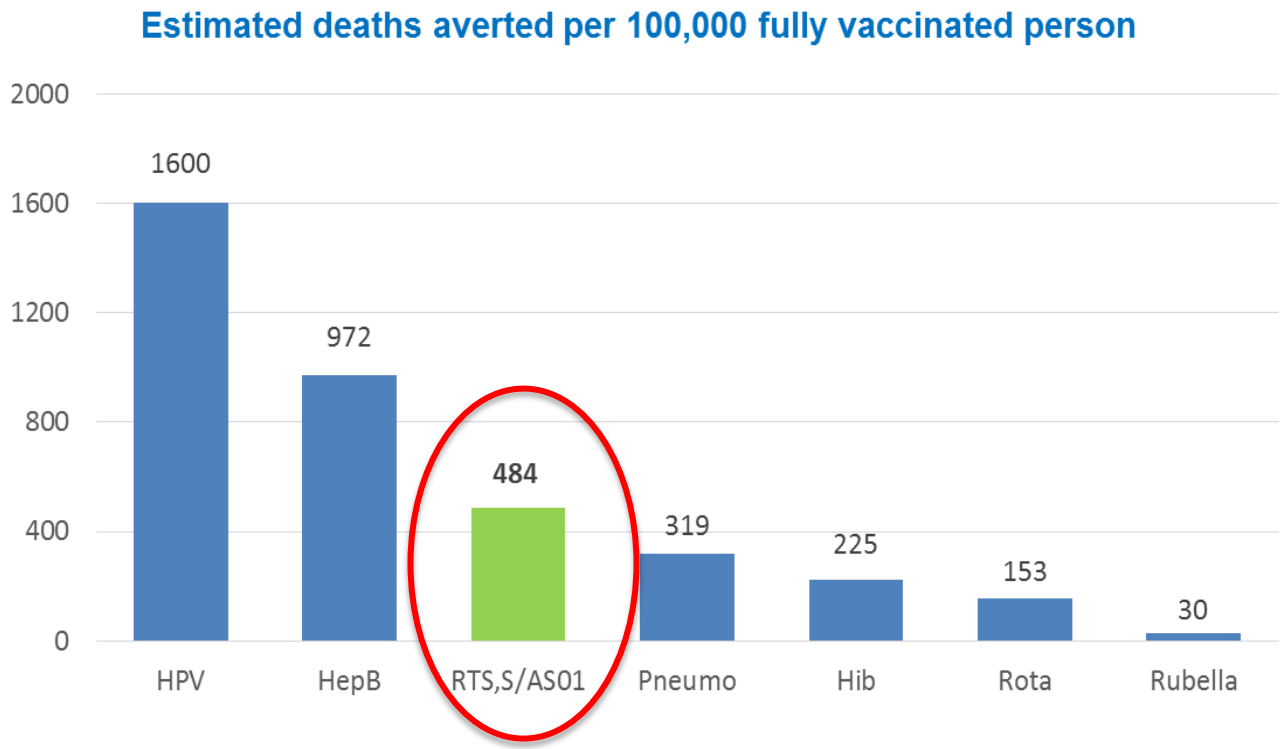
200 children fully vaccinated

233 malaria cases prevented

1 death prevented

Source: Penny MA, et al. Public health impact and cost-effectiveness of RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. Lancet 2016.

Potential Number of Deaths Averted per 100,000 Fully Vaccinated Persons Compares Favorably With Other Gavi-supported Vaccines



Source: For RTS,S/AS01: Penny MA, Verity M, Bever CA, et al. Public health impact and cost-effectiveness of RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. Lancet 2016.
All other vaccines: Estimated deaths averted per FVP over 2015-2030 based on Gavi Strategic Demand Forecast v.11, 2014 impact analysis

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