RTS,S Malaria Vaccine Implementation Programme

A joint initiative of GMP & IVB

Update to the Malaria Policy Advisory Committee

David Schellenberg, Scientific Advisor, GMP
Mary Hamel, Coordinator MVIP, IVR, IVB
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Background

• RTS,S - 30 years in development, a Phase 3 trial in >16,000 children, positive scientific opinion from the European Medicines Agency

• SAGE and MPAC unequivocal on the need to determine the public health role of this vaccine

• The RTS,S Malaria Vaccine Implementation Programme (MVIP) is a joint project between WHO’s Global Malaria Programme and the Immunization, Vaccines and Biologicals Department, developed in collaboration with participating countries, PATH and GSK

• Proposal submitted to funding agencies mid-2016
  – Design based on WHO technical consultation in January 2016
Update since September 2016
Funding Situation: Phase 1 (2017-2020)

• June 2016:
  – Gavi Board approved up to $27.5 million for the first 4 years, on condition of matched funding
  – UNITAID Executive Board approved strategic fit

• September 2016:
  – UNITAID committed up to $9.6 million for Phase 1

• November 2016:
  – Global Fund committed $15 million

• Expect to sign funding agreements in coming weeks
Update since September 2016
In-country preparations

• First round of joint WHO/PATH/GSK visits to 3 countries in October-November 2016
  – Continued interest at technical and leadership levels confirmed

• Countries officially informed of selection

• Second round of visits in March 2017
  – Work started to plan vaccine introduction, routine pharmacovigilance strengthening and evaluation components

• Public announcement planned for World Malaria Day
Update since September 2016
Regulatory review

• 18-19 February 2017: Pre-AVAREF meeting convened representatives from National Regulatory Agencies of the 3 pilot countries.
• Potential regulatory strategies discussed to authorise use of RTS,S in pilots
• Suggestion for joint regulatory review process to be facilitated by WHO
Update since September 2016
Evaluation protocol & selection of evaluation partners

• Master protocol developed, to be submitted by GSK as part of their Risk Management Plan
• Country-specific protocols to be developed following selection of in-country evaluation partners
• Request for Proposals to select evaluation partners will be published in coming weeks
  – Expect to confirm evaluation partners by Q2/Q3 2017
• Potential for joint ethics review of protocol facilitated by WHO under discussion
Malaria Vaccine Pilot Implementation

Overall design (1)

• **Sub-national introduction of the approved RTS,S vaccine**
  – Introduced and delivered by EPI using existing mechanisms
  – In close collaboration with NMCP, ensuring continued use of other malaria prevention and treatment measures

• **Sub-national introduction enables some areas (clusters) to introduce RTS,S at the beginning of the programme, while other clusters act as comparison areas**
  – Allocation of clusters into implementation or comparison areas will be randomized
  – Clusters defined (e.g. district, sub-country) based on country context and evaluation requirements
Rigorous Evaluation, by country-based research institutions, of:

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

Essential that standardised monitoring systems are set up in RTS,S and comparison areas to record outcomes of interest
Illustration of cluster-randomized design

1. Identification of pilot area targeting approx. 240,000 children in ~ 60 clusters (≈4000 children/cluster) + 4 additional clusters for Phase IV

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

3. Randomization of clusters

- RTS,S implementation
- Comparison areas
SAFETY EVALUATION
Malaria Vaccine Implementation Programme

Key safety questions

• What is the frequency and profile of RTS,S/AS01 reported AEFI?
• Is administration of RTS,S associated with rare or unexpected adverse events?
• Is RTS,S/AS01 vaccination associated with an increased risk of meningitis or cerebral malaria?
• Is RTS,S/AS01 vaccination associated with gender specific mortality?
• Is the relative impact of RTS,S/AS01 positive overall?
  – Some risks may be present, as with other vaccines, but are the risks outweighed by benefits such that the overall impact is beneficial?
3 pillars of RTS,S safety assessment in the MVIP

<table>
<thead>
<tr>
<th>MOH Strengthened Pharmacovigilance</th>
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<tbody>
<tr>
<td>Passive / enhanced passive / active</td>
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<tr>
<td>All Pilot areas: N=240,000*</td>
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<tr>
<td>All AEFI, includes rare/unanticipated AEFI; AESI</td>
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<td>Gender specific mortality</td>
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<table>
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<tr>
<th>WHO Pilot Evaluation</th>
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<tr>
<td>In-Patient Surveillance</td>
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<tr>
<td>Active</td>
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<tr>
<td>8 clusters: N=32,000*</td>
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<td>Focus on meningitis and cerebral malaria</td>
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<tr>
<th>GSK Phase IV Study</th>
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<td>Active with HH visits</td>
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<tr>
<td>4 clusters: N=16,000*</td>
</tr>
<tr>
<td>Focus on meningitis, malaria, as well as AESI</td>
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* Half of N located in vaccinated clusters, half in unvaccinated clusters. A sample of at least 240,000 children, including the first 120,000 children vaccinated in each country, will contribute to the evaluation.
MVIP safety evaluation for RTS,S

**Routine spontaneous AEFI reporting**
Focus on rare and unexpected AEFI

**Pilot evaluation in-patient surveillance**
Focus on meningitis and cerebral malaria

**Phase IV in-patient surveillance**
Focus on meningitis, cerebral malaria and AESIs

Strengthened in **all** areas

8 sentinel hospitals

4 sentinel hospitals + home visits
Paediatric Inpatient Surveillance

• Quality assured, inpatient surveillance at sentinel hospitals
• Systematic, standardised clinical and laboratory assessment and management of all admissions

• All under 5 year admissions to paediatric wards:
  – Demographic and vaccination data, outcome of admission
  – Key clinical signs, including criteria for lumbar puncture
  – Lab results: malaria status, CSF results

• Relevant clinical staff trained in inpatient management algorithm
  – Includes collection of blood and CSF samples to assess study endpoints
  – Standardised case definitions
Statistical Considerations

• Sample size of 96,000 across the pilot implementation countries

• 12 clusters of 4,000 births per arm will detect a 2.1 fold increase in meningitis
  – Assumes meningitis rate in comparison areas of ~0.1% from age 6-35m (inter-cluster correlation coefficient=0.4)
    • If meningitis rate is lower (0.04%), able to detect a 2.6 fold increase
IMPACT EVALUATION
Objectives of impact evaluation

• To assess the impact of the RTS,S vaccine on:
  – all cause child mortality (overall and by gender)
  – malaria-specific mortality
  – severe malaria

• Implementation in the setting of concomitant recommended malaria interventions
Proposed approach: Mortality surveillance at community level

• Network of Village Reporters (VR) documents all deaths among children aged up to 48 months in the implementation & comparison areas
  – Dependent on country-specific practices, VRs will either:
    • Visit all households in their catchment area regularly, or
    • Build and maintain a network to ensure VRs are informed of fatal events among children

• Deaths in the age range have a standardized, WHO-approved Verbal Autopsy (VA) performed, according to locally acceptable practices

• All deaths and VAs are reported to the local Evaluation Partner(s), national coordinating bodies & national vital statistics registry / CRVS

• Community-based data complemented by cause-specific hospital data
Statistical Considerations

• 240,000 children per country (120,000 in RTS,S areas and 120,000 in comparison areas) should enable detection of a 10% reduction in mortality
  – Assumes ~2.5% mortality from 6 – 35 months of age in those not vaccinated
    • Inter-cluster coefficient of variation of 0.1
  – 80% power, 5% significance level

• Final analysis of impact occurs at the end of the follow-up period
FEASIBILITY EVALUATION
**Feasibility evaluation components**

Endpoints

- Coverage and contextual indicators
- Health economic assessments
- Vaccine availability & process indicators

**Preparation**

- Household Survey (baseline)
- PIE Survey*
- Household survey (primary series)
- Household Survey (fourth dose)
- Micro-costing tool to assess cost of delivery
- Health care utilisation survey

**Doses 1, 2, 3**

Continuous monitoring of immunization coverage using administrative data

**Dose 4**

- Updated PHI CE estimates
- Budget impact assessments

Approximate timings in 1 country. Countries are likely to start pilot implementation activities within 6 months of each other
Overview of Pilot Implementation of RTS,S/AS01

- **First children receive RTS,S/AS01**
- **Continuous vaccine coverage, morbidity, mortality & safety monitoring**
  - Household Survey*
  - Household Survey**
  - Household Survey***
- **Continuous vaccine coverage, morbidity, mortality & safety monitoring**
- **Comparison Areas**
- **RTS,S Introduction**
- **Intervention Areas**
- **Last children in evaluation cohort receive RTS,S/AS01 dose 4**
- **Follow up of evaluation cohort complete**
- RTS, S vaccinations continue in intervention & comparison areas pending decision to roll out or terminate

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

Dose 1
Dose 2
Dose 3
Dose 4

* RTS,S/AS01 availability & process indicators
** RTS,S/AS01 primary course coverage & contextual indicators
*** RTS,S/AS01 dose 4 coverage & contextual indicators
Key aspects that need to be ready before vaccine introduction

- Regulatory review
- Vaccine implementation
- Country-specific protocols & their ethical review
- Evaluation readiness – following RFP-based selection of Evaluation Partners
  - Baseline household survey
  - Sentinel hospital clinical surveillance
  - Community mortality surveillance
- Pharmacovigilance

Readiness for all these aspects is a pre-requisite for programme start
Indicative overall timeline 2017-2022
Target: first vaccine introduction Q2 2018

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<thead>
<tr>
<th>Year</th>
<th>Phase 1</th>
<th>Phase 2</th>
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<tbody>
<tr>
<td>2017</td>
<td>Planning and start-up period</td>
<td>Analysis &amp; policy period</td>
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<td>2018</td>
<td>Evaluation period</td>
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<td>2019</td>
<td>RTS,S launch</td>
<td>Review of final data by WHO advisory bodies</td>
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<td>2020</td>
<td>First children receive 4th dose</td>
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<tr>
<td>2021</td>
<td>Evaluation cohort fully vaccinated</td>
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<tr>
<td>2022</td>
<td>RTS,S introduction in comparison areas (if desired)</td>
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**Preparation**
- Household surveys
- Feasibility evaluation
- Impact evaluation
- Ongoing safety monitoring

**Vaccination**
- Vaccine implementation in RTS,S clusters
- Continue (if desired)
Co-ordination with GSK’s Phase IV Study

• Regular interactions WHO, PATH, GSK since April 2016
  – Bi-weekly leadership call, weekly Protocols & Methods sub-group calls, communications sub-group calls

• Tripartite collaboration agreement being finalised

• Initial joint WHO/PATH/GSK country visits Oct/Nov 2016
  – Introduction to WHO-led and Phase IV evaluations

• Master protocol for the WHO-led evaluation developed by WHO, reviewed by PATH & GSK
  – WHO protocol to be included in GSK’s Risk Management Plan submitted to European Medicines Agency
Conclusion

• RTS,S/AS01 – the first malaria vaccine
  – 39% reduction in clinical malaria
  – 31% reduction in severe malaria
  – Considerable potential for public health impact

• WHO recommendation to pilot implementation in 3 countries: rigorous evaluation of feasibility, safety and impact

• Master protocol to form basis of country-specific protocols

• Target date for start of vaccinations: Q2:2018
  – Discussion needed on duration of RTS,S deployment in implementation areas, and potential roll out of RTS,S/AS01

Over 4 years follow-up