WHO Malaria Vaccine Technology Roadmap

Landmark: By 2015, develop and license a first-generation *P. falciparum* malaria vaccine that has a protective efficacy of more than 50% against severe disease and death and lasts longer than one year.

By 2030, license vaccines targeting *P. falciparum* and *P. vivax*
- Development of malaria vaccines with a protective efficacy of at least 75% against clinical malaria for at-risk groups in endemic areas
- Development of malaria vaccines that reduce transmission of the parasite. This will enable elimination in multiple settings through administration in mass campaigns
The 60+ years global quest for a malaria vaccine

The challenge:
- Protozoan with a large genome: 14 chromosomes, 5-6000 genes
- Multistage life cycle with stage specific expression of proteins
- Allelic and antigenic variation/polymorphism
- Human immune response is complex and genetically variable

Pre-erythrocytic vaccine
Antibodies and cellular immune response to:
- Prevent infection of liver cells
- Protect against blood-stage infection with impact on clinical disease

Blood-stage vaccine
Antibodies to interfere with merozoites and infected erythrocytes:
- Impact on clinical disease

Transmission-blocking vaccine
Antibodies to interfere with parasite development in the mosquitoes:
- No impact on clinical disease
- Elimination strategy

More than a dozen CS-based antigens were tested in humans between 1988 and 1995. All strategies to modify CS to promote better immune responses, including the use of adjuvant systems, either failed or did not increase efficacy against challenge.

The circumsporozoite protein:
✓ is the major surface protein of the sporozoite
✓ helps the parasite bind to liver cells
Making the circumsporozoite protein immunogenic: RTS,S

The RTS,S candidate vaccine particles:
- The R and T regions from CSP are fused to the hepatitis B surface antigen (HBsAg).
- The fusion protein is co-expressed with HBsAg in yeast (Saccharomyces cerevisiae) where they spontaneously assemble into mixed non-infectious virus-like particles.


GSK’s adjuvanted vaccine design principle

RTS,S/AS01 malaria vaccine

RTS,S antigen

Specificity of the immune response

AS01 adjuvant system

Designed to enhance and modulate the immune response to the antigen. Combines the effect of two or more immune-enhancers.

The goal is to select the right antigen - adjuvant system combination which can guide the immune response, delivering enhanced and sustained protection

Impact of enhanced antigen purification on vaccine immunogenicity and tolerability

**Empirical approach**
Observation based
Jenner

**Pathogen-based**
Replicating
(live attenuated pathogen)

Non-replicating
(whole inactivated pathogen)

Subunit
(toxoids, split virus, fragments of pathogens)

Purified antigens
(various antigens, recombinant proteins)

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**Immunogenicity**

**Tolerability**

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Defense triggers required to induce immune response

Microbial structures contain:

- **Antigens** (antigens alone may exhibit insufficient immunogenicity)
- **Defense Triggers** ("Danger Signals"), e.g. PAMPs (pathogen-associated molecular patterns), that act as intrinsic immune-triggers

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The RTS,S malaria vaccine development programme: A 30-year effort from GSK and successful partnerships

1984
GSK/WRAIR initiate collaboration

1987
RTS,S first created by combining the malaria CS protein and hepatitis B surface antigen

1984–1991
Preclinical testing

1995
First clinical tests begin in adults in US

1997
Key proof-of-concept study shows 6 out of 7 volunteers in challenge trial are fully protected

1998
First trial in Africa begins in the Gambia

2001
GSK/MVI partnership initiated

2004
Key proof-of-concept study in children in Mozambique

2007
Phase II results in African children and infants

2009
Phase III efficacy study start

2010
First Phase III efficacy results in 12–17 months old over 12 months of follow-up

2011
Key Phase II efficacy results in African children and infants

2012
Second Phase III efficacy results in 6–12 weeks old over 12 months of follow-up

2013
Third Phase III efficacy results over 18 months of follow-up and per study site

2015
Final Phase III efficacy results including 3–4 years of follow-up and effect of 4th dose of RTS,S

1987–2001
Preclinical and phase I testing

2001–2011
Phase II testing

2011–2015
Phase III testing

1995–2012
17,000 children and infants

1995–2012
4,100 clinical sites

1995–2012
12,000 volunteers

1995–2012
500 million doses

Unprecedented breakthrough in malaria vaccine development!

First Proof of Concept for efficacy of the RTS,S vaccine candidate against Plasmodium falciparum infection

Human challenge model at the Walter Read Army Institute of Research

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>IgG</th>
<th>CMI</th>
<th>Protected</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>-</td>
<td>-</td>
<td>0/6</td>
</tr>
<tr>
<td>RTS,S/AS04</td>
<td>+</td>
<td>+</td>
<td>1/8</td>
</tr>
<tr>
<td>RTS,S/AS03</td>
<td>+++</td>
<td>+</td>
<td>5/7</td>
</tr>
<tr>
<td>RTS,S/AS02</td>
<td>+++</td>
<td>+++</td>
<td>6/7</td>
</tr>
</tbody>
</table>

The most efficacious formulation is the one that consistently induced the best humoral and cell-mediated immune responses in preclinical testing. Unprecedented breakthrough in malaria vaccine development!

RTS,S/AS01 a potentially improved candidate vaccine formulation

- In animal models and clinical studies, several antigens appeared more immunogenic (particularly for cellular immunity) when formulated with AS01, with little change in reactogenicity
- In a phase II/IIa challenge study, RTS,S/AS01 induced higher antibody response and higher CD4+ cell response than RTS,S/AS02

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Protected</th>
<th>Infected</th>
<th>VE</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTS,S/AS02</td>
<td>14</td>
<td>30</td>
<td>31.8% (95% CI: 17.6; 47.6)</td>
</tr>
<tr>
<td>RTS,S/AS01</td>
<td>18</td>
<td>18</td>
<td>50.5% (95% CI: 32.9; 67.1)</td>
</tr>
</tbody>
</table>

VE AS01 vs VE AS02: p = 0.11

AS01 was introduced into the clinical development plan of RTS,S with aim to improve vaccine efficacy and duration of protection

Summary of pediatric Phase II findings

- Consistent efficacy (40-50%) in different malaria transmission settings in Kenya, Mozambique, Tanzania, Gabon & Ghana:
  - Trend toward higher efficacy in younger children (with less natural immunity)
  - Evidence for efficacy against severe forms of the disease
  - Beneficial effect on clinical disease up to 42 months after the last vaccine dose
- Acceptable safety profile:
  - Over 8,000 doses of RTS,S/AS02 or RTS,S/AS01 administered to more than 3,000 children/infants aged between 6 weeks and 6 months
  - Reactogenicity pattern comparable to control vaccines (including EPI vaccines)
  - Trend towards clinical benefit on all cause morbidity and mortality
- Can be co-administered within routine infant EPI immunizations (compatible in terms of safety, efficacy & immune responses)

GSK-MVI partnership decision to initiate phase III with RTS,S/AS01
Phase III multicentre efficacy trial of RTS,S/AS01

- Double-blind, randomized, controlled trial.
- 11 centres in 7 African countries.
- **Wide range of malaria transmission intensities** by site: 0.03-4.27 clinical episodes per infant during first 12 months of follow-up.
- 15,459 children enrolled in two age categories:
  - Children aged 5–17 months (8,922)
  - Infants aged 6–12 weeks (6,537)
- Infants received the study vaccine **co-administered** with routine vaccines (DTPw-HepB/Hib+OPV).
- High access to health care, malaria diagnostics and treatment (ACT).
- High ITN usage throughout the study: close to 80% in children and somewhat higher in infants.

**Comparator vaccines:**
- Rabies vaccine in children 5-17 months of age at first dose
- Men C conjugate vaccine in infants 6-12 weeks of age at first dose and both age categories at Month 20

Median follow-up until study end:
- 48 months post Dose 1 (range: 41-55) for children 5-17 months of age at first dose
- 38 months post Dose 1 (range: 32-46) for infants 6-12 weeks of age at first dose

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**Phase III efficacy study design**

**Randomization 1:1:1**

- **Screening:**
  - R: RTS,S/AS01 at Month 0,1,2
  - C: Comparator at Month 0,1,2

- **Follow-up to M20 (before 4th dose)**
  - Comparing R3R+R3C vs C3C

- **All subjects followed to M32**

- **End of long term follow-up**
  - All subjects followed to M32

**Comparator vaccines:**
- Rabies vaccine in children 5-17 months of age at first dose
- Men C conjugate vaccine in infants 6-12 weeks of age at first dose and both age categories at Month 20
### RTS,S/AS01 vaccine efficacy against clinical malaria

<table>
<thead>
<tr>
<th>Age at vaccination</th>
<th>Vaccine Efficacy* against clinical malaria over the first 12 months of follow-up</th>
<th>Vaccine Efficacy against clinical malaria over the entire study period (46 mo of FU**)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 to 17 months (children)</td>
<td>RTS,S 51% (47;55)</td>
<td>RTS,S 39% (34;43)</td>
</tr>
<tr>
<td>6 to 12 weeks (infants)</td>
<td>RTS,S 33% (26;39)</td>
<td>RTS,S 27% (21;32)</td>
</tr>
<tr>
<td>M0</td>
<td>RTS,S control</td>
<td>RTS,S control</td>
</tr>
<tr>
<td>M1</td>
<td>M2</td>
<td>(36 mo of FU**)</td>
</tr>
<tr>
<td>M20</td>
<td>RTS,S control</td>
<td>RTS,S control</td>
</tr>
</tbody>
</table>

* VE % (95% CI) in ATP cohort from 3rd dose; ** median duration of follow-up from dose 3 to study end

RTS,S Clinical Trials Partnership. NEJM 2011; NEJM 2012; Lancet 2015; European SmPC

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### RTS,S/AS01 vaccine efficacy against severe malaria

<table>
<thead>
<tr>
<th>Age at vaccination</th>
<th>Vaccine Efficacy* against severe malaria over the first 12 months of follow-up</th>
<th>Vaccine Efficacy against severe malaria over the entire study period (46 mo of FU**)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 to 17 months (children)</td>
<td>RTS,S -45% (22;60)</td>
<td>RTS,S 29% (6;46)</td>
</tr>
<tr>
<td>6 to 12 weeks (infants)</td>
<td>RTS,S -37% (5;58)</td>
<td>RTS,S 21% (-7;42)</td>
</tr>
<tr>
<td>M0</td>
<td>RTS,S control</td>
<td>RTS,S control</td>
</tr>
<tr>
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<tr>
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RTS,S Clinical Trials Partnership. NEJM 2011; NEJM 2012; Lancet 2015; European SmPC
RTS,S/AS01 vaccine efficacy against malaria hospitalizations

<table>
<thead>
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<th>Vaccine Efficacy* against malaria hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>over the first 12 months of follow-up</td>
</tr>
<tr>
<td></td>
<td>over the entire study period (46 mo of FU**)</td>
</tr>
<tr>
<td>5 to 17 months</td>
<td><strong>RTS,S</strong></td>
</tr>
<tr>
<td>(children)</td>
<td>48% (35;59)</td>
</tr>
<tr>
<td></td>
<td><strong>RTS,S</strong></td>
</tr>
<tr>
<td></td>
<td>12% (-5;26)</td>
</tr>
<tr>
<td>6 to 12 weeks</td>
<td><strong>RTS,S</strong></td>
</tr>
<tr>
<td>(infants)</td>
<td>32% (7;50)</td>
</tr>
<tr>
<td></td>
<td><strong>RTS,S</strong></td>
</tr>
<tr>
<td></td>
<td>27% (7;43)</td>
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</tr>
<tr>
<td></td>
<td>13% (-9;31)</td>
</tr>
<tr>
<td></td>
<td><strong>control</strong></td>
</tr>
<tr>
<td></td>
<td>37% (24;49)</td>
</tr>
<tr>
<td></td>
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<td></td>
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</table>

* VE % (95% CI) in ATP cohort from 3rd dose; ** median duration of follow-up from dose 3 to study end
RTS/S Clinical Trials Partnership, NEJM 2011; NEJM 2012; Lancet 2015; European SmPC

Importance to complement Vaccine Efficacy estimates with estimates of potential Public Health Impact

Vaccine efficacy needs to be translated into public health impact in order to understand the true absolute value of vaccination:

Example: The effect of Human Rotavirus Vaccine on severe rotavirus gastroenteritis in the first year of life in Malawi and South Africa

<table>
<thead>
<tr>
<th>Malawi</th>
<th>South Africa</th>
</tr>
</thead>
<tbody>
<tr>
<td>49 %</td>
<td>77 %</td>
</tr>
<tr>
<td>131</td>
<td>54</td>
</tr>
<tr>
<td>67</td>
<td>42</td>
</tr>
</tbody>
</table>
Phase III results indicate a potential major public health impact of RTS,S/AS01

- The clinical results showed that RTS,S/AS01 has the potential to provide considerable public health impact when used in combination with other control measures.
- Although vaccine efficacy was lower in 6-12 week-old infants, meaningful public health benefits might still be provided in areas with high disease burden.

Tolerability and safety profile of RTS,S/AS01: >11,000 children evaluated in clinical trials

- **Adverse events (AEs):**
  - Most common solicited AEs: fever (27%), irritability (14%) and local injection site reactions such as pain (16%) and swelling (7%).
  - Most serious AEs: febrile seizures (within 7 days post-vaccination).
  - Other AEs: decreased appetite, somnolence, diarrhoea, vomiting and injection site induration.

- **Serious adverse events (SAEs) occurred at similar frequency between groups in the Phase III clinical study:**

<table>
<thead>
<tr>
<th></th>
<th>5-17 months</th>
<th>6-12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R3R</td>
<td>R3C</td>
</tr>
<tr>
<td>Any SAE</td>
<td>24%</td>
<td>25%</td>
</tr>
<tr>
<td>Fatal SAEs</td>
<td>2.0%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

Frequency of related SAEs was low: ≤0.3% for RTS,S, mainly febrile seizures.
Impact of RTS,S/AS01 on mortality

- Phase III study was not designed to show impact on mortality:
  - In clinical trial setting, good and fast access to health care reduces mortality
  - Children enrolled in the Phase II trial in Siaya (Kenya) experienced a 70% reduction in all-cause mortality compared to children not in the trial (1)
- The low mortality rate hampers interpretation of mortality endpoints, especially subgroup analysis that further reduce the statistical power
- Gender-specific mortality was analysed post-hoc, upon request: (2)
  - All-cause mortality in girls across both age categories:
    - 2.4% with RTS,S (123 / 5,091) vs 1.3% in control group (33 / 2,603)
    - Risk Ratio: 1.91 (1.30 – 2.79)
  - Such a difference was not observed in boys (1.8% vs. 2.2%)
  - None of the fatalities were considered as related to vaccination
  - Causes of death are multiple and not related to one single event
  - Results could have been affected by several confounders


Example: impact of Rotavirus vaccination on mortality

Clinical Trials
- No increased risk of intussusception was observed
- No benefit on mortality was demonstrated in the large phase III trial (1)
- A potential imbalance of deaths due to pneumonia was observed between rotavirus and control vaccine recipients

Post Marketing Surveillance
- A study in Mexico showed a small increased risk of intussusception, but no increased risk of fatal pneumonia after rotavirus vaccination (2)
- A significant decline in diarrhea-related deaths among Mexican children was observed after introduction of rotavirus vaccination (3)
  - Infants <12 mo of age: ♀ mortality -41%
  - Children 12 to 23 mo (vaccine coverage ~4%): ♀ mortality -29%

(1) Cheuvart B. et al. PIDJ 2009; (2) Velázquez R. et al. PIDJ 2012; (3) Richardson et al. NEJM 2010
Observations during the RTS,S/AS01 Phase III clinical trial that require further investigation in phase IV studies

- Numerical imbalance of meningitis cases in 5-17 month old age category:
  - 21 in ± 6,000 children vaccinated with RTS,S/AS01 vs. 1 in ± 3,000 controls over 4 years of follow-up
  - No similar imbalance in the 6-12 weeks infant age category:
    - 12 in ± 4,000 infants vaccinated with RTS,S/AS01 vs.
    - 6 in ± 2,000 controls over 3 years of follow-up
  - Different etiologies, no clustering in time-to-onset, probably a chance finding

- Trend for more severe malaria after 18 months of follow-up in children who did not receive a 4th dose of RTS,S/AS01, compatible with rebound

- Numerical imbalance of hospitalized severe malaria with coma (BCS ≤ 2):
  - Compatible with cerebral malaria, but diagnosis not clinically confirmed
  - Time-to-onset not suggesting a direct effect of vaccination, nor an indirect effect related to rebound
  - Overall impact on severe malaria remained positive in children having received 4 vaccine doses

- To be further evaluated during phase IV studies and pilot implementations

EMA positive opinion for RTS,S/AS01 (Mosquirix™)

(July 2015)

- Positive scientific opinion was granted in July 2015 by the European Medicines Agency (EMA) following the review of the quality, safety and efficacy of RTS,S/AS01 under Article 58 (candidate manufactured, but not for use, in European Union) in collaboration with WHO:

  - Mosquirix™ is indicated for active immunization of children aged 6 weeks up to 17 months against malaria caused by Plasmodium falciparum and against hepatitis B
    - Mosquirix™ should not be used for the prevention of hepatitis B in settings where prevention against malaria caused by P. falciparum is not sought.
  - The use of Mosquirix™ should be based on official recommendations considering P. falciparum malaria epidemiology in different geographical areas
    - The use of other malaria control measures recommended locally should not be interrupted

- Positive opinion conditional upon GSK’s commitment to deliver Phase IV study programme specified in the Risk Management Plan (RMP)
Summary of safety endpoints addressed in Phase IV
As described in the RMP agreed with (or to be submitted to) EMA *

<table>
<thead>
<tr>
<th>Data source</th>
<th>Important identified risks</th>
<th>Important potential risks</th>
<th>Missing information</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPI-MAL-002</td>
<td>Febrile convulsion</td>
<td>• Meningitis</td>
<td>• Effectiveness and impact of RTS,S/AS01 on clinical malaria, severe malaria, cerebral malaria and mortality</td>
</tr>
<tr>
<td>EPI-MAL-003</td>
<td></td>
<td>• Hypersensitivity (including anaphylaxis)</td>
<td>• Fever upon co-administration with other EPI vaccines known to induce fever (DTPw-based combination vaccines and PCV)</td>
</tr>
<tr>
<td>WHO pilots*</td>
<td></td>
<td>• Potential Immune Mediated Diseases (pIMDs)</td>
<td>• Safety in HIV-infected children</td>
</tr>
<tr>
<td>Malaria-076</td>
<td></td>
<td>• Rebound effect</td>
<td>• Long-term efficacy</td>
</tr>
<tr>
<td>EPI-MAL-003</td>
<td></td>
<td>• Cerebral malaria</td>
<td>• Impact on mortality (overall and by gender)*</td>
</tr>
<tr>
<td>WHO pilots*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPI-MAL-005</td>
<td></td>
<td>• Behavioural changes on usage of other malaria preventive measures</td>
<td>• P. falciparum strain replacement</td>
</tr>
<tr>
<td>EPI-MAL-010</td>
<td></td>
<td></td>
<td>• Plasmodium species replacement</td>
</tr>
<tr>
<td>WHO pilots*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaria-073</td>
<td></td>
<td></td>
<td>• Immunogenicity of RTS,S/AS01 when co-administered with Measles, Yellow fever and Rubella vaccines</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Cross immunization against human catalase</td>
</tr>
</tbody>
</table>

* Changes to the Risk Management Plan (RMP) to be submitted to EMA


Mathematical modelling provides additional insight in the potential public health impact (PHI) of RTS,S/AS01

- Four different modelling groups provided PHI estimates for RTS,S/AS01:
  - PHI is reasonably predicted by the mean \( \text{PfPR}_{2-10} \) in a country
  - PHI is projected to be greatest in settings with \( \text{PfPR}_{2-10} >10\% \), although positive even at \( \text{PfPR}_{2-10} \) of 5-10%

**Modelling of 4 doses of RTS,S given to children 6 months or older, living in region of \( \text{PfPR}_{2-10} \) between 10-65%, predicts that over a 15-year period:**
- 1 malaria death can be prevented per approx. 200 vaccinated children
- 230 clinical malaria cases can be prevented per 200 vaccinated children

- Other factors influencing overall PHI and cost-effectiveness are:
  - Vaccine efficacy profile (including duration of protection)
  - Vaccine coverage in real-life settings (including drop off between doses)
  - Changes in insecticide resistance, or anti-malarial resistance
  - Changes in access to treatment
  - Vaccine price

\( \text{PfPR}_{2-10} \): *P. falciparum* parasite prevalence in children aged 2-10 years; Penny et al, Lancet 2015
**Mosquirix™: the start of the next journey**
From vaccine to vaccination

**WHO recommendation for RTS,S/AS01 (January 2016)**
Joint advice from SAGE² and MPAC³ adopted by WHO in Nov 2015

- Pilot implementation in 3-5 settings in sub-Saharan Africa with moderate-to-high transmission of malaria
  - 3 doses of vaccine between ages 5-9 months, fourth dose 15-18 months later

- Projects should address:
  - Risk-benefit in real-life setting
  - Feasibility of a 4-dose schedule and coverage of current tools for malaria control
  - Impact of RTS,S/AS01 on mortality

- WHO is working with experts, PATH and GSK on:
  - Design of pilot implementations
  - Country selection
  - Resource mobilization

- Phase 4 studies and pilot implementations will be complementary

---

1) [WHO WER January 2016](http://www.who.int/wer/2016/wer9104.pdf?ua=1)
2) Strategic Advisory Group of Experts on Immunization
3) Malaria Policy Advisory Committee
Pilot implementation projects and Phase IV studies

Plan to have pilot implementation projects in 3 countries
Per country:
- Randomization into vaccinated and unvaccinated clusters
- 30 clusters / arm (approximately 120,000 subjects / arm)
- 4 clusters / arm with sentinel hospital (SH) (16,000 subjects / arm)

The journey towards the RTS,S/AS01 malaria vaccine candidate
CONCLUSION (1/2)

- Malaria remains a major public health threat, especially in young children living in sub-Saharan Africa
- The addition of a malaria vaccine to existing interventions could help to achieve improved and sustained malaria control
- Results from clinical trials indicate that RTS,S/AS01 has the potential to help protect young children living in P. falciparum-endemic regions from malaria and its consequences
  - Over the first year after vaccination, RTS,S/AS01 reduced the number of malaria cases by half in children and by one third in infants
  - Vaccine efficacy was highest shortly after vaccination and waned over time, but could be enhanced by a fourth dose
- Clinical results to date indicate that RTS,S/AS01 has an overall acceptable tolerability and safety profile
The journey towards the RTS,S/AS01 malaria vaccine candidate
CONCLUSION (2/2)

• RTS,S/AS01 has the potential to provide considerable public health impact when used in combination with other control measures, especially in areas of higher malaria transmission

• It is important that the proposed implementation studies take place, to ensure continued investment in malaria vaccine development and in other drugs and vaccines for tropical diseases

• This new malaria intervention could have a major role to play in future malaria control programs, provided the phase IV studies and pilot implementation projects show that the safety profile of the RTS,S/AS01 vaccine is acceptable, give reassurance with regard to the meningitis and cerebral malaria safety signals, and confirm the feasibility of delivering RTS,S/AS01 according to a four-dose schedule

• In addition, experience gained during the development, evaluation and deployment of RTS,S/AS01 will be important for future new malaria vaccines

Acknowledgments

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Study staff
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Malaria Clinical Trials Alliance

Research Centers and Partners
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Ifakara Health Institute, Bagamoyo, Tanzania
Institut de Recherche en Science de la Santé, Nanoro, Burkina Faso
KEMRI/CDC Research and Public Health Collaboration, Kisumu, Kenya
KEMRI-Walter Reed Project, Kombewa, Kenya
KEMRI - Wellcome Trust Research Program, Kilifi, Kenya
Kintampo Health Research Center, Kintampo, Ghana
National Institute for Medical Research, Korogwe, Tanzania
School of Medical Sciences, Kumasi, Ghana
University of North Carolina Project, Lilongwe, Malawi
University of Tübingen, Germany
Prince Leopold Institute of Tropical Medicine, Belgium
University of Copenhagen, Denmark
University of Barcelona, Spain
Swiss Tropical Institute, Switzerland
London School of Hygiene and Tropical Medicine, UK
US Centers for Disease Control and Prevention, USA
University of North Carolina at Chapel Hill, USA
Walter Reed Institute of Research, USA