Le vaccin anti-paludique RTS,S en éssais cliniques de phase 3

Académie Nationale de Pharmacie
Séance thématique du mardi 21 avril 2010

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GlaxoSmithKline Biologicals

The intolerable burden of malaria

- 250 million malaria cases per year, 86% in Africa
- 1 million deaths per year, 90% in Africa
- Mostly children under 5 years
- Leading cause of death from a single infectious agent
- Cost US$12 billion and loss of 1.3% of economic growth annually in Africa
**Fighting against malaria: tools available today**

**Preventive**
- Insecticide Treated bedNets (ITNs) and Long-Lasting Insecticidal Nets (LLINs)
- Indoor Residual Spraying (IRS) and other Vector Controls
- Intermittent Preventive Treatment (IPT)
  - in pregnancy (IPTp)
  - in infancy (IPTi) or children (IPTc)

**Curative**
- Anti-malarial Drug Treatment (ACT, Artemisinin Combinations Therapy)
- Improved Malaria Case Management (RDTs, Rapid Diagnostic Tests)

**The need for a malaria vaccine**
- Important malaria disease burden, but those with the greatest need can least afford current prevention and control measures
- Challenges to Malaria Control in the SSA setting:
  - Parasite resistance to drugs
  - Mosquito resistance to insecticides
  - HIV co-infection
  - Climate change increasing suitable mosquito habitats
  - Inadequate infrastructure for delivery of control measures
  - Low compliance to protective measures
- Additional tools (such as a malaria vaccine channeled through EPI) would help to meet public health policy goals and targets

*WHO IVR 2005, WHO 2008 malaria report, RBM GMAP 2008*
The development of a malaria vaccine

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

... but feasible
- Acquisition of natural immunity against disease in individuals living in endemic regions
- Protective immunity has been achieved in several malaria animal models (by active immunization as well as passive transfer of monoclonal antibodies and T cells)
- Passive transfer of protection by purified immunoglobulins obtained from immune adults
- Active immunization of mice and humans with radiation-treated sporozoites confers sterile immunity

Plasmodium falciparum life cycle
Pre-erythrocytic malaria vaccines

- Pre-erythrocytic malaria vaccines (sporozoites and intra-hepatic parasites): prevent infection and/or reduce incidence and severity of disease
- Protection against pre-erythrocytic parasites requires:
  - Humoral antibody responses against sporozoites to block invasion of hepatocytes
  - Cellular CD4+ (Th1) and CD8+ (CTL) T lymphocyte responses to kill intra-hepatic parasites and/or destroy infected liver cells through γ-INF secretion or via direct cytotoxicity

☞ Protection against infection
☞ Impact on clinical disease

The RTS,S pre-erythrocytic antigen

Circumsporozoite Protein:
- Major surface protein of the sporozoite
- Involved in binding of sporozoite to liver cells

Generation of RTS,S virus-like particles
Co-expression of RTS (fusion protein) and HBS protein in Saccharomyces cerevisiae. Spontaneously assemble into mixed virus-like particles (VLP)

The Adjuvant System

- Designed to induce strong antibody and Th-1 cell mediated immune responses

- Immunostimulants:
  - QS21: Saponin extract of *Quillaja saponaria*
  - MPL: Monophosphoryl Lipid A

with:
- Oil-in-water emulsion (= AS02)
- Liposome suspension (= AS01)

Clinical development with both adjuvant systems in parallel
⇒ select the best one for phase III

Objectives of the RTS,S Malaria Vaccine Candidate Development Program

- Develop a vaccine that will protect infants and children residing in malaria endemic regions from clinical disease and severe malaria resulting from *Plasmodium falciparum* infection
- Safe and well tolerated
- Compatible with standard EPI vaccines (DTP, HBV, Hib, OPV…)
- Implementable through existing delivery programs such as the EPI
- Complements existing malaria control measures
### History of RTS,S/AS development and major milestones

- **2000**: Initiation of paediatric development
- **2001**: Start phase III Efficacy Study with AS01 in Children and Infants (Africa)
- **2002**: Start of the RTS,S program in Belgium
- **2003**: PoC AS02 in Infants (Africa)
- **2004**: Proof of Concept (PoC) in Gambian Adults
- **2005**: PoC AS02 in Children (Africa)
- **2006**: PoC AS02 in Infants EPI co-ad (Africa)
- **2007**: PoC AS01 in Children (Africa)
- **2008**: PoC AS02 in Infants (Africa)
- **2009**: Process development, GMP manufacturing & Scaling Up
- **2010**: Preclinical Immunology and Adjuvant Systems R&D work

### First Proof of Concept (PoC) for efficacy of the RTS,S vaccine against P. falciparum infection

<table>
<thead>
<tr>
<th>Vaccine</th>
<th># Challenged</th>
<th># Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>RTS,S/AS04</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>RTS,S/AS03</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>RTS,S/AS02</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

The most efficacious formulation is the one that consistently induced the best humoral and CMI responses in preclinical testing.

Consistent efficacy of RTS,S candidate vaccine against *P. falciparum* in human challenge model

**Percent with sterile protection (pooling)**

<table>
<thead>
<tr>
<th>Dose</th>
<th>n</th>
<th>VE (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 dose</td>
<td>10</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>2 doses</td>
<td>33</td>
<td>47</td>
<td>-25</td>
</tr>
<tr>
<td>3 doses</td>
<td>142</td>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>185</td>
<td>45%</td>
<td>0</td>
</tr>
</tbody>
</table>

45% efficacy against infection in laboratory challenge model


Objectives of phase 2 pediatric program

- Evaluation of efficacy and preliminary assessment of the duration of efficacy
- Evaluation of safety in children/infants
- Feasibility of EPI integration
- Dose, Schedule, Adjuvant System selection

11 studies in infants and children, in Sub-Saharan Africa
### Efficacy of RTS,S/AS02 in 1 to 4 year old children (N~2000, Mozambique)

<table>
<thead>
<tr>
<th>Vaccine Efficacy</th>
<th>%</th>
<th>95% CI</th>
<th>p-value</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. falciparum</em> infection</td>
<td>45</td>
<td>31-56</td>
<td>&lt; 0.001</td>
<td>6 m</td>
</tr>
<tr>
<td>Clinical malaria</td>
<td>35</td>
<td>22-47</td>
<td>&lt; 0.0001</td>
<td>18 m</td>
</tr>
<tr>
<td>Severe malaria</td>
<td>49</td>
<td>12-71</td>
<td>0.02</td>
<td>18 m</td>
</tr>
<tr>
<td>Hospitalized malaria</td>
<td>31</td>
<td>4-50</td>
<td>0.032</td>
<td>18 m</td>
</tr>
<tr>
<td>All clinical episodes</td>
<td>26</td>
<td>12-37</td>
<td>&lt; 0.001</td>
<td>42 m</td>
</tr>
<tr>
<td>Severe malaria</td>
<td>38</td>
<td>3-61</td>
<td>0.045</td>
<td>42 m</td>
</tr>
<tr>
<td>Parasite prevalence</td>
<td>34*</td>
<td>12-50</td>
<td>0.0043</td>
<td>42 m</td>
</tr>
</tbody>
</table>

* % reduction in prevalence of parasitaemia at 42 mo cross-sectional survey

Alonso et al, Lancet 2004;364:1411-20  

### Efficacy of RTS,S/AS01 in 5 to 17 month old children (N=894, Kenya & Tanzania)

<table>
<thead>
<tr>
<th>Vaccine Efficacy</th>
<th>%</th>
<th>95% CI</th>
<th>p-value</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st clinical episode</td>
<td>53</td>
<td>28-69</td>
<td>&lt; 0.001</td>
<td>8 m</td>
</tr>
<tr>
<td>All clinical episodes</td>
<td>56</td>
<td>31-72</td>
<td>&lt; 0.001</td>
<td>8 m</td>
</tr>
<tr>
<td>1st clinical episodes</td>
<td>39</td>
<td>20-54</td>
<td>&lt; 0.001</td>
<td>12 m</td>
</tr>
<tr>
<td>All clinical episodes</td>
<td>42</td>
<td>22-57</td>
<td>&lt; 0.001</td>
<td>12 m</td>
</tr>
</tbody>
</table>

* in Kenya only

<table>
<thead>
<tr>
<th>Vaccine Efficacy</th>
<th>%</th>
<th>95% CI</th>
<th>p-value</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st clinical episode</td>
<td>46</td>
<td>24-61</td>
<td>&lt; 0.001</td>
<td>17 m</td>
</tr>
<tr>
<td>All clinical episodes</td>
<td>51</td>
<td>29-66</td>
<td>&lt; 0.001</td>
<td>17 m</td>
</tr>
</tbody>
</table>

Bejon et al 2008 NEJM 359: 24: 2521-32  
Ally Olotu et al. MIM 2009
**Efficacy of RTS,S/AS02 in African infants**

- 220 infants randomized in Mozambique
- RTS,S at 10,14,18 weeks of age with DTPw/Hib + OPV at 8,12,16 weeks

<table>
<thead>
<tr>
<th>Vaccine Efficacy</th>
<th>%</th>
<th>95% CI</th>
<th>p-value</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. falciparum</em> infection</td>
<td>66</td>
<td>43-80</td>
<td>&lt; 0.0001</td>
<td>3 m</td>
</tr>
<tr>
<td>1st clinical episode*</td>
<td>66</td>
<td>25-84</td>
<td>0.007</td>
<td>3 m</td>
</tr>
</tbody>
</table>

340 infants randomized in Tanzania
- RTS,S at 8,12,16 wks, co-administered with DTPw/Hib + OPV

<table>
<thead>
<tr>
<th>Vaccine Efficacy</th>
<th>%</th>
<th>95% CI</th>
<th>p-value</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. falciparum</em> infection</td>
<td>65</td>
<td>21-85</td>
<td>0.012</td>
<td>6 m</td>
</tr>
<tr>
<td>1st clinical episode*</td>
<td>43</td>
<td>-47-78</td>
<td>0.24</td>
<td>6 m</td>
</tr>
</tbody>
</table>

*Exploratory endpoint*

*Aponte et al. Lancet 2007; 370: 1543-51*

*Abdulla et al. NEJM 2008; 359: 2533-44*

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**Conclusion RTS,S/AS Phase 2 Efficacy Results**

- Consistent and significant efficacy observed
  - versus infection, clinical episodes & severe malaria
  - in different transmission settings
  - in the different ages groups evaluated
  - with and without EPI co-administration

- Clinical benefit extending up to 42 months following vaccination in Mozambique

- Based on these Phase 2 results, RTS,S has the potential to have a major impact on the burden of malaria
Reactogenicity following RTS,S/AS01 or control vaccination
(in 5 to 17 month old children, N=894, Kenya & Tanzania)

Solicited local and general symptoms (7 days post vaccination)

- Pain
- Swelling
- Drowsiness
- Irritability
- Fussiness
- Loss of appetite
- Fever (≥37.5°C)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>RTS,S/AS01 (N=447)</th>
<th>Rabies vaccine (N=447)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Swelling</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Irritability</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Fussiness</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Loss of appetitie</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Fever (≥37.5°C)</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

* Pain: cried when limb was moved/spontaneously painful; Swelling >20mm; Drowsiness that prevented normal activity; Irritability/Fussiness: Crying that could not be comforted/prevented normal activity; Loss of appetite: not eating at all; Fever: axillary temp >39.0°C

SAEs following RTS,S/AS01 or control vaccination
(in 5 to 17 month old children, N=894, Kenya & Tanzania)

Indication of non malaria specific protection
Severe malaria disease following RTS,S/AS01 or control vaccination (in 5 to 17 month old children, N=894, Kenya & Tanzania)

Bejon et al 2008 NEJM 359; 24: 2521-32

Indication of higher protection against the more severe forms of disease

RTS,S safety and tolerability profile

- Over 8,000 doses of RTS,S/AS02 or AS01 administered to more than 3,000 children/infants (6 wks to 6 yrs of age)
- Reactogenicity pattern comparable to control vaccines including routine EPI vaccines
- Laboratory safety monitoring: no apparent safety signal
- Favourable assessment of differences in frequency of SAEs (RTS,S vs control)

**RTS,S immune responses**

- **Strong antibody response** to the *P. falciparum* circumsporozoite (CS) repeat domain (anti-CS) in all age groups
- **Anti-CS antibodies** consistently associated with protection against infection in the adult challenge model and in field trials with children and infants, but no correlate of protection could be defined.
- **Anti-CS antibody levels** wane over time, but remain significantly higher compared to control groups up to 42 months after the last vaccine dose
- **Robust CS-specific CD4 T-cell responses** induced in malaria naïve adult volunteers and associated with protection against infection in challenge model (Kester et al. JID 2009)

**Summary of Phase 2 findings**

- **Unprecedented and consistent efficacy** demonstrated in different transmission settings in Kenya, Mozambique and Tanzania
  - Beneficial effect on clinical and severe disease up to 42 months after the last vaccine dose
  - Trend toward higher efficacy against severe forms of disease
  - Trend toward higher efficacy with the AS01 Adjuvant System (Kester et al. JID 2009; Bejon et al. NEJM 2008)
- **Favorable safety & reactogenicity profile**
  - 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)
- **Induction of CS-specific humoral and cell mediated immune responses** shown to be associated with protection against infection

« GO » FOR PHASE 3!
Phase III efficacy trial

- Up to 16,000 children
  6 to 12 weeks or 5 to 17 months old
- 11 centers in 7 African countries with different transmission settings
- Malaria control measures optimized
- Key safety & efficacy data to support file for regulatory authorities
- Full evaluation of relevant disease and public health endpoints to inform planning for implementation
- Significant capacity building investment
- Designed in collaboration with GSK, MVI and the Clinical Trials Partnership Committee, with feedback from WHO, FDA and EMEA

Today: ±9,000 children enrolled

Phase 3 Efficacy Objectives

- **Co-primary objectives:**
  - Efficacy against clinical malaria disease over 1 year post dose 3 in:
    - Children aged 5 to 17 months
    - Infants aged 6 weeks at first dose (EPI co-administration)

- **Secondary objectives:**
  - Efficacy against severe malaria disease
  - Prevention of malaria hospitalization
  - Prevention of anemia
  - Efficacy against clinical malaria in different transmission settings
  - Duration of efficacy to 2.5 years post dose 3
  - Requirement for a booster dose
  - Efficacy against fatal malaria and all-cause mortality
  - Efficacy against other serious illness
  - All-cause hospitalization, sepsis and pneumonia

Conclusion from clinical studies to date

- The RTS, S vaccine is the first and only malaria vaccine candidate to demonstrate efficacy in young children and infants exposed to intense Plasmodium falciparum transmission.

- If phase 3 data are consistent with phase 2 results and RTS, S is licensed and widely implemented, the vaccine could have a major societal, economic and public health impact in malaria-endemic regions in Sub-Saharan Africa.

Acknowledgements

- **Collaborating Institutions**
  - **Southern**
    - Institut de Recherche en Science de la Santé, Nanoro, Burkina
    - Kumsai Centre for Collaborative Research, Ghana
    - School of Medical Sciences Kumasi, Ghana
    - Kintampo Health Research Centre, Ghana
    - Albert Schweitzer Hospital, Gabon
    - Kenya Medical Research Institute, Kilifi, Kenya
    - Wellcome Collaborative Research Programme, Kilifi, Kenya
    - Kenya Medical Research Institute, Kisumu, Kenya
    - University of North Carolina Project, Lilongwe, Malawi
    - Centro de Investigação em Saude de Manhiça, Mozambique
    - Ifakara Health Research Development, Tanzania
  - **Northern**
    - Prince Leopold Institute of Tropical Medicine, Belgium
    - University of Copenhagen, Denmark
    - University of Tuebingen, Germany
    - Bernhard Nocht Institute, Germany
    - University of Barcelona, Spain
    - Swiss Tropical Institute, Switzerland
    - London School of Hygiene & Tropical Medicine, UK
    - University of North Carolina at Chapel Hill, USA
    - Walter Reed Army Institute of Research, USA
    - Center for Disease Control and Prevention, USA

- My numerous colleagues in the Malaria team at GSK Biologicals
- The Malaria Vaccine Initiative at PATH: our partner in this endeavour
- The Malaria Clinical Trial Alliance: for support to several trial sites and
- The volunteers, their families and their communities: for their participation in the trials