Development of a Malaria Vaccine for Sub-Saharan African Children

December 3, 2009
Lode Schuerman
Agenda

Malaria
  – Disease burden
  – Prevention and vaccine development

RTS,S vaccine
  – Vaccine design
  – Phase I early development
  – Phase II: overview of results
  – Phase III study design
Millions of children still die from preventable infectious diseases

- Malaria 28%
- HIV 9%
- Tuberculosis (TB) 1%
- Pneumococcus 17%
- Yellow Fever, Diptheria, Polio, Hep B 0%
- Pertussis 7%
- Measles 13%
- Hib 9%
- Rotavirus 10%
- Meningococcus A/C, Japanese Encephalitis 1%
- Tetanus 5%

WHO World Health Report 2004
The intolerable burden of malaria

3.3 billion people at risk, 50% of the world’s population

250 million malaria cases per year, 86% in Africa

109 endemic countries, 45 within WHO African region

1 million deaths per year, 90% in Africa

Plasmodium falciparum is the most severe form

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

Areas where malaria transmission occurs
Areas with limited risk of malaria transmission
No malaria

This map is intended as a visual aid only and not as a definitive source of information about malaria endemicity.

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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)

Recent trends in malaria incidence

**Zanzibar (Tanzania)**

- What caused these trends?
  - Usage of RDT?
  - Implementation of LLIN?
  - Treatment by ACT?
  - Improved health care (training)?
  - Changes in rainfall pattern and climate (droughts)?
  - Changes in health information systems (in Zanzibar for example all other causes of hospitalization also decreased)?

**Rwanda**

- In Rwanda, malaria incidences increased again in 2008-09...
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

A malaria vaccine will be an essential component of future malaria prevention and control measures

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 stage
  - Sporozoites
  - Liver-stage parasites
- Sexual blood stage
  - Gametocytes
- Asexual blood or erythrocytic stage
  - Merozoites
  - Rupturing schizont
  - Schizont
  - Trophozoite
Malaria
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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 (DTPw, HBV, Hib, OPV…)

✔ Implementable through existing delivery programs such as the EPI

✔ Complements existing malaria control measures
The RTS,S pre-erythrocytic antigen

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)

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

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


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

### Human challenge model at the Walter Read Army Institute of Research

<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><strong>RTS,S/AS02</strong></td>
<td><strong>7</strong></td>
<td><strong>1</strong></td>
</tr>
</tbody>
</table>

Antibodies against the CS protein of *Plasmodium falciparum* in vaccinated volunteers

- Different RTS,S vaccine formulations with different Adjuvant Systems
- Antibody responses against tandem-repeat epitopes (ELISA with recombinant R32LR)

![Graph showing antibody responses against tandem-repeat epitopes](image)

Cell mediated immune responses in vaccinated volunteers

IFN$\gamma$ responses in volunteers immunized with different formulations of RTS,S and association with protective efficacy

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- **Phase II: overview of results**
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Efficacy of RTS,S/AS against malaria in African children (supported by PATH-MVI)

Unprecedented and significant reduction of clinical & severe malaria episodes, across different malaria transmission settings

Clinical benefit extending over 42 months following vaccination

Could have a major impact on burden of malaria

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<table>
<thead>
<tr>
<th>Population (age)</th>
<th>Vaccine Efficacy</th>
<th>Efficacy</th>
<th>Significance (p-value)</th>
<th>Duration of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4 years(^1,2,3)</td>
<td>Clinical malaria</td>
<td>35%</td>
<td>&lt;0.001</td>
<td>18 months</td>
</tr>
<tr>
<td></td>
<td>Severe malaria</td>
<td>49%</td>
<td>0.02</td>
<td>18 months</td>
</tr>
<tr>
<td></td>
<td>Hospitalized malaria</td>
<td>31%</td>
<td>0.032</td>
<td>18 months</td>
</tr>
<tr>
<td></td>
<td>All clinical episodes</td>
<td>26%</td>
<td>&lt;0.001</td>
<td>42 months</td>
</tr>
<tr>
<td></td>
<td>Severe malaria</td>
<td>38%</td>
<td>0.045</td>
<td>42 months</td>
</tr>
<tr>
<td>5-17 months(^4)</td>
<td>Clinical malaria</td>
<td>53%</td>
<td>&lt;0.001</td>
<td>8 months</td>
</tr>
<tr>
<td></td>
<td>All clinical episodes</td>
<td>56%</td>
<td>&lt;0.001</td>
<td>8 months</td>
</tr>
<tr>
<td>10 weeks(^5)</td>
<td>Clinical malaria</td>
<td>66%</td>
<td>0.007</td>
<td>3 months</td>
</tr>
<tr>
<td>8 weeks(^6) (+EPI)</td>
<td>Clinical malaria</td>
<td>43%</td>
<td>0.24</td>
<td>6 months</td>
</tr>
</tbody>
</table>

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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)

<table>
<thead>
<tr>
<th>Condition</th>
<th>RTS,S/AS01(012) + DTPw-HepB/Hib (N = 170)</th>
<th>DTPw-HepB/Hib (N = 171)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>22.9 (17 – 30)</td>
<td>21.1 (15 – 28)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>11.2 (7 – 17)</td>
<td>8.2 (5 – 13)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6.5 (3 – 11)</td>
<td>5.8 (3 – 11)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>3.5 (1 – 8)</td>
<td>8.2 (5 – 13)</td>
</tr>
<tr>
<td><em>P. falciparum</em> infection</td>
<td>2.9 (1 – 7)</td>
<td>9.4 (5 – 15)</td>
</tr>
<tr>
<td>URTI</td>
<td>2.4 (1 – 6)</td>
<td>3.5 (1 – 8)</td>
</tr>
<tr>
<td>Impetigo</td>
<td>1.8 (0 – 5)</td>
<td>2.3 (1 – 6)</td>
</tr>
</tbody>
</table>

SAEs occurring within 8 months of follow-up, in at least 2% of subjects in any of the vaccine groups

Agnandji et al MIM 2009
**Anti-CS 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!
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Phase 3 multi-center efficacy trial

- 11 centers in 7 African countries
- Sites represent different malaria transmission settings
- Up to 16,000 children in 2 age categories:
  - 6 weeks to 12 weeks in EPI co-ad
  - 5 to 17 months
- Designed in collaboration with scientific community, with feedback of MALVAC*, WHO, FDA, EMEA and African National Regulatory Agencies

*Moorthy V. et al. Vaccine 2008
**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

*uncertain power

Duration of efficacy

- Duration of efficacy up to 30 months post primary series
  - Time periods: overall, pre and post booster
  - Assessed as efficacy against first episodes and all episodes

- Evaluation of requirement for a booster at 18 months post primary
  - Evaluated as efficacy post booster

R = RTS,S/AS01  C = Control vaccine

Conclusion from clinical studies to date

The RTS,S vaccine is the first malaria vaccine candidate to demonstrate that young children and infants exposed to intense *Plasmodium falciparum* transmission can be protected from infection and malaria disease.

If this vaccine is licensed (after the level of efficacy across various transmission settings has been clarified in the ongoing phase 3 study), it could have a major societal, economic and public health impact in malaria-endemic regions in Sub-Saharan Africa.

Clinical development conducted in partnership with PATH-Malaria Vaccine Initiative, GSK and:

- Institut de Recherche en Science de la Santé, Nanoro, **Burkina Faso**
- Kumasi Centre for Collaborative Research & School of Medical Sciences Kumasi, **Ghana**
- Kintampo Health Research Centre, **Ghana**
- Albert Schweitzer Hospital
- KEMRI-Walter Reed Project
- KEMRI-Wellcome Trust Research Programme
- KEMRI/CDC Research and Training Centre
- University of North Carolina Project, **Malawi**
- Centro de Investigação em Saúde de Manhiça, **Mozambique**
- Ifakara Health Research Development Centre, **Tanzania**
- National Institute of Medical Research, **Tanzania**
- 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**
- Center for Disease Control and Prevention, **USA**
- University of North Carolina at Chapel Hill, **USA**
- Walter Reed Army Institute of Research, **USA**

In collaboration with the Malaria Clinical Trials Alliance