Development of Malaria Vaccines

WHO PDVAC Meeting 8-10th June 2016

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Malaria Burden & existing Interventions

- 214 million malaria cases in 2015, 88% in Africa
- 438,000 deaths in 2015, 90% in Africa
- Three biggest risks:
  - Financing fragility
  - Artemisinin resistance
  - Insecticide resistance

Figure 5.3 Proportion and number of people not receiving an intervention, sub-Saharan Africa, 2014

- Vector control: Live in a household with at least one ITN or covered by IRS, 269 million people
- IPTp: Pregnant women receive at least one dose of IPTp, 15 million pregnant women
- Treatment for malaria: Children with malaria receive an ACT, 68-80 million children with malaria

Figure 5.16 Reported pyrethroid resistance status of malaria vectors, measured with insecticide bioassays since 2010

Data shown are for standard bioassays. Where multiple insecticide classes or types, mosquito species or time points were tested, the highest resistance status is shown.

Source: National malaria control programme reports, African Network for Vector Resistance, Malaria Atlas Project, President’s Malaria Initiative (United States), scientific publications.
Road Map New Vision

“Safe and effective vaccines against *Plasmodium falciparum* and *Plasmodium vivax* that prevent disease and death, and prevent transmission to enable malaria eradication.”

- Expands to include *P. vivax* in addition to *P. falciparum*
- Expands to all geographical regions rather than sub-Saharan Africa alone
- Expands to include target groups beyond children alone depending on goal and risk groups

[www.who.int/immunization/topics/malaria/vaccine_roadmap/en/](http://www.who.int/immunization/topics/malaria/vaccine_roadmap/en/)
Two new Strategic goals

By 2030, license vaccines targeting *Plasmodium falciparum* and *Plasmodium vivax* that encompass the following two objectives, for use by the international public health community:

1. **Development of malaria vaccines** with protective efficacy of at least 75 percent **against clinical malaria** suitable for administration to appropriate at-risk groups in malaria-endemic areas.

2. **Development of malaria vaccines** that reduce transmission of the parasite and thereby substantially reduce the incidence of human malaria infection. This will enable elimination in multiple settings. **Vaccines to reduce transmission** should be suitable for administration in mass campaigns.

www.who.int/immunization/topics/malaria/vaccine_roadmap/en
Malaria Vaccines design: Points of intervention

Target stage

- Gametocytes
- In mosquito gut
- Sporozoites
- LIVER
- Merozoites

Clinical effect

- Prevent infection and disease
- Reduce clinical disease severity
- Interrupt transmission
Global malaria vaccine pipeline

**Phase 1a**: ChAd63/MVA ME-TRAP + Matrix M™, PfCelTOS FMP012, PfPEBS, ChAd63/MVA PvDBP, Pfs25-VLP

**Phase 2a**: RTS,S-AS01 ChAd63/MVA ME-TRAP, RTS,S-AS01 fractional dose

**Phase 1b**: ChAd63/MVA MSP 1, FMP2.1/AS01B, P27A

**Phase 2b**: Pfs25-EPA, AMA1-DiCo, PfSPZ

**Phase 3**: ChAd63/MVA ME-TRAP, RTS,S-AS01

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**Completed, Reporting overdue**

- Ad35.CS/Ad26.CS
- Polypeptide DNA EP 1300 Phase 1a
- ChAd63/MVA (CS, TRAP, AMA)
- EBA 175.R2 Phase 1b
- MSP3 [181-276] Phase 2b

*P. falciparum* vaccines: Pre-erythrocytic, Blood-stage, Transmission-blocking

*P. vivax* vaccines: Pre-erythrocytic, Blood-stage, Transmission-blocking

RTSS Phase 3 Trial in Africa

Randomized, controlled, double-blind trial designed to evaluate vaccine efficacy, safety, reactogenicity, and immunogenicity in children up to 32 months after the administration of the first dose of vaccine.

Two age categories:
- Children 6-12 weeks of age: 7100
- Children 5-17 months of age: 8900

11 centers in 7 African countries

Trial implemented with optimized vector control and malaria treatment

The co-primary endpoints of the trial are: vaccine efficacy against clinical malaria after 12 months of follow-up in each age category.
Impact of RTS,S/AS01 on clinical malaria over 18 months of follow-up

**Vaccine Efficacy (% and 95%CI)**

- **5-17 months**
  - 46% VE$^{1^*}$

- **6-12 weeks**
  - 27% VE$^{1^*}$

**Number of cases averted (per 1000 children vaccinated)**

- 941 cases averted (47 to 2356)$^{2^*}$
- 444 cases averted (-12 to 1429)$^{2^*}$

**Incidence in control group**

(number of episodes per person year at risk)
WHO recommends Large scale Pilot implementation of RTSS in Africa

• WHO recommends the pilot implementations of the 4-dose schedule of the RTS,S/AS01 vaccine in 3–5 distinct epidemiological settings in sub-Saharan Africa, at subnational level, covering moderate-to-high transmission settings,” with three doses administered to children between 5 and 9 months of age, followed by a fourth dose 15–18 months later.

• Pilots to involve sufficiently large populations also to assess,
  1. feasibility of providing all four doses of RTS,S to the target age group through existing health services;
  2. impact of RTS,S on child mortality;
  3. evidence of any causal relationship between RTS,S and either meningitis or cerebral malaria, in the context of surveillance of adverse events; as well as the compilation of evidence on the functioning of country immunization programs and the use of currently recommended malaria control measures.
Malaria Vaccine Multi-component

Four Stages for Vaccines to Target

1. Sporozoite Stage
   - R21 VLP

2. Liver Stage
   - Viral vectors

3. Blood Stage
   - Pfs25 VLP
   - PfRH5 VLP

4. Mosquito Stage
   - Within mosquito gut
R21 compared to RTS,S

RTS,S

- Produced in *S. cerevisiae*
- In Phase III trial
- Efficacy << 50% in field trials

R21

- Produced in *P. pastoris*
- Very high immunogenicity in mouse model
- 100% efficacy in transgenic challenge in mice
- Phase I trials (matrix M, AS01)
Initial R21 Clinical Trial Data
5-fold dose sparing with R21 in matrix-M compared to RTS,S in AS01

Phase IIa challenge trial planned for September 2016

Ventakraman, Bowyer et al. unpublished
Liver-Stage Vaccines
Two advances entering trials

1. More protective antigens
   • LSA1 and LSAP2 (in viral vectors)

2. Prime & Target Immunization
   • Adenoviral vector administered i.m. followed by targeting immunisation that redirects CD8+ T cells to the liver
   • Greater efficacy observed pre-clinically
Clinical Progression of PfRH5 Vaccine Candidates

1. ChAd and MVA vectors phase I
   - Complete

2. Protein PfRH5
   - GMP manufacture complete
   - Phase I/IIa planned

3. VLP for PfRH5
   - Pre-clinical
**Pfs25-IMX313 Nanoparticle**

Antigen fused to IMX313 self-assembles to form a heptamer

Log improvement in antibody titre

![Graph showing log improvement in antibody titre](image)

- 5 ug protein in Alhydrogel i.m.
- Phase I trial of Pfs25-IMX313 in viral vectors underway
- GMP manufacture of Pfs25-IMX313 nanoparticle funded

Significantly better transmission-blocking activity in the Standard Membrane Feeding Assay

![Graph showing transmission-blocking activity](image)
Deploying a Multi-Stage Malaria Vaccine
Virus-Like Particles + Vectors in Infants

**A Regime for Deployment in Infants in Developing Countries**

<table>
<thead>
<tr>
<th>Month</th>
<th>Ad</th>
<th>MVA</th>
<th>R+</th>
<th>R+</th>
<th>R+</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>ChAd63</td>
<td>MVA MeTRAP</td>
<td>R+</td>
<td>R+</td>
<td>R+</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>2</td>
<td></td>
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<tr>
<td>3</td>
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<td>4</td>
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<tr>
<td>5</td>
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<td>6</td>
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<tr>
<td>7.5</td>
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<tr>
<td>9</td>
<td></td>
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</tr>
</tbody>
</table>

Ad = ChAd63 MeTRAP  
MVA = MVA MeTRAP  
R+ = R21 + RH5 + Pfs25  
all VLPs in adjuvant
Whole Malaria Sporozoite Vaccine approaches

Irradiated infected mosquitoes showed > 90% protection 40 years ago

Whole sporozoite vaccines
- Radiation attenuated
- Chemo attenuated
- Genetically attenuated

Currently using mosquitoes to produce the sporozoites in the future by invitro culture
Irradiated purified sporozoite provide Short Term Homologous Protection - CHMI 3 Weeks Post Last Dose, Pf3D7 by Mosquito Bite

<table>
<thead>
<tr>
<th>Study</th>
<th>Dosage Regimen</th>
<th>Number of Volunteers</th>
<th>Protecte</th>
<th>Challenged</th>
<th>Protective Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PfSPZ/ Dose (x 10⁵)</td>
<td>Numbe r of Doses</td>
<td>Total No. PfSPZ (x 10⁵)</td>
<td>Volunte ers</td>
<td></td>
</tr>
<tr>
<td>VRC 314/ WRAIR 2080</td>
<td>2.7</td>
<td>3</td>
<td>8.1</td>
<td>3</td>
<td>10*</td>
</tr>
<tr>
<td>VRC 314</td>
<td>2.7</td>
<td>4</td>
<td>10.8</td>
<td>7</td>
<td>9**</td>
</tr>
<tr>
<td>(R. Seder, K. Lyke)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WRAIR 2080 (J. Epstein)</td>
<td>2.7</td>
<td>5</td>
<td>13.5</td>
<td>12</td>
<td>13***</td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td>3</td>
<td>13.5</td>
<td>13</td>
<td>15***</td>
</tr>
<tr>
<td></td>
<td>(8 week interval)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7/8*, 5/6**, and 6/6*** controls developed parasitemia

WRAIR and Sanaria
Irradiated Sporozoites provide durable Homologous and Heterologous Protection

<table>
<thead>
<tr>
<th>Study</th>
<th>Dosage Regimen</th>
<th>Number of Volunteers at 23-24 Weeks</th>
<th>Protective Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PfSPZ/Dose (x 10^5)</td>
<td>Total No. PfSPZ (x 10^5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number of Doses</td>
<td>Protecte d</td>
<td>Challeng ed</td>
</tr>
<tr>
<td>VRC 314</td>
<td>2.7</td>
<td>10.8</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>6</td>
<td>55%*</td>
</tr>
<tr>
<td>WRAIR 2080</td>
<td>2.7</td>
<td>13.5</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>7</td>
<td>70%</td>
</tr>
<tr>
<td>WRAIR 2080</td>
<td>4.5</td>
<td>13.5</td>
<td>87%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>8</td>
<td>57%</td>
</tr>
</tbody>
</table>

*All Protected at 12 Months

9.0 x 10^5 PfSPZ three times at 8 week intervals

- 9/14 (64\%) vaccinees and 0/6 controls were protected: Pf3D7 CHMI (homologous) at 19 weeks after last dose of PfSPZ Vaccine
- 5/6 (83\%) vaccinees who were protected at 19 weeks and 0/6 controls were protected: Pf7G8 CHM (heterologous at 33 weeks
## Irradiated Sporozoites provide durable Heterologous Protection in adults in Africa

<table>
<thead>
<tr>
<th>Study Location</th>
<th>Vaccine</th>
<th>Sample size (N)</th>
<th>Follow-up From Last Vaccine Dose (weeks)</th>
<th>Protective Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>Immunized</td>
<td>Time-to-Event Analysis* (95% C.I.)</td>
<td>Significance (p-value)</td>
</tr>
<tr>
<td>Kenya</td>
<td>RTS,S/ AS01B</td>
<td>75</td>
<td>74</td>
<td>49.3%</td>
</tr>
<tr>
<td>Mali</td>
<td>PfSPZ Vaccine</td>
<td>44</td>
<td>42</td>
<td>93.2%</td>
</tr>
</tbody>
</table>

* Time to Event Analysis = Vaccine efficacy based on survival analysis/Cox hazard ratio

** Proportional Analysis = (\(AR_C - AR_V\) / \(AR_C\)) * 100%, where \(AR\) = attack rate

*** Polhemus et al., 2009 PLoS ONE 4(7): e6465. doi:10.1371/journal.pone.0006465

\[ MRTC \text{ and } Sanaria \]
Chemoprophylaxis with Sporozoites (CPS)  
Roestenberg NEJM 2009

• Pf sporozoites administered by bite of mosquitoes
• 3 sequential monthly doses of 12-15 mosquito bites (total of only 36-45 infected mosquito bites)
• Weekly chloroquine
• 100% protection after malaria challenge
## Purified Sporozoites with Chloroquine Results - Tübingen

B. Mordmueller, P. Kremsner

<table>
<thead>
<tr>
<th>Group</th>
<th>Dosage Regimen</th>
<th>Number of Volunteers</th>
<th>Protective Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PfSPZ/Dose (x 10³)</td>
<td>Number of Doses (x 10³)</td>
<td>Protected</td>
</tr>
<tr>
<td>1</td>
<td>3.2</td>
<td>9.6</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>12.8</td>
<td>38.4</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>51.2</td>
<td>153</td>
<td>9</td>
</tr>
</tbody>
</table>

*U. Tubingen and Sanaria*
Malaria Vaccine Evaluation Models
## CHMI models

<table>
<thead>
<tr>
<th>Mimicking natural route of infection</th>
<th>Sporozoite – mosquito bite</th>
<th>Sporozoite – injection</th>
<th>Blood-stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to control inoculum size</td>
<td>+/-</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Life-cycle stages amenable to study</td>
<td>Sporozoite (skin and blood)</td>
<td>Sporozoite (blood) Liver-Stage Blood-Stage</td>
<td>Blood-Stage</td>
</tr>
<tr>
<td>Availability</td>
<td>Limited trial centers</td>
<td>Potential for widespread use</td>
<td>Potential for widespread use</td>
</tr>
<tr>
<td>Duration of blood-stage parasite exposure</td>
<td>Short (2–4 d)</td>
<td>Variable (2–8 d)</td>
<td>Longer (8–9 d)</td>
</tr>
<tr>
<td>Reliably achieves 100% infection</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

Sheehy et al Hum Vaccin Immunother 2013
Some issues with Controlled Human Malaria Infections

- CHMI harmonization of methods and end points for comparison of products
- Comparisons of Mosquito versus and Purified sporozoite malaria infections
- Questions addressed by Sporozoite versus Blood stage
- Extension of studies in endemic areas and prediction of field results
- Adaptive designs for quick selection of products, approaches and optimization
- Modified designs for exploration of biology and immune mechanisms and responses
Issues for field Evaluations

• Harmonization of designs and end points
• Adaptive designs that move products quickly
• Standard of care and Choice of controls
• Prediction of public health impact
• Exploration of immune responses and mechanisms

Ogwang C et al 2015
Harmonization immunology

Example PfCSP Antibody Responses

WRAIR 2080 vs 14-I-N010 (Mali)

- Compared PfCSP antibody titers after 5 doses of $2.7 \times 10^5$ PfSPZ
- Consistently higher responses in WRAIR 2080

WRAIR, MRTC and Sanaria
Some take home messages

• Current malaria control and elimination tools do not provide complete protection.
• First generation malaria vaccine on track to licensure. This partially efficacious malaria vaccine is of benefits in public health setting especially in high burden areas.
• Second generation vaccines are expected to provide even higher protection
• Delivery and approaches to public health use of the vaccines will need to be addressed in the development path
• Harmonization of tools and procedures will improve understanding of performance of candidates and possible mechanisms
Asante Sana