Malaria
Update on Vaccine Development Progress and Future Directions

Patrick E. Duffy, M.D.
The Problem of Malaria: Better but still Bad

- In 2014, 97 countries and territories had ongoing malaria transmission
  - 3.2 billion people are at risk of malaria, 1.2 billion are at high risk
  - In high-risk areas, more than one malaria case occurs per 1000 population
- Disease burden in 2013
  - ~198 million cases of malaria worldwide, ~ 584 000 deaths
  - 90% of all malaria deaths occur in Africa
- Pregnant women and young children are particularly vulnerable to the disease
  - ~437 000 African children died before their fifth birthday due to malaria

Three biggest threats
- Artemisinin resistance
- Insecticide resistance
- Financing fragility
Key malaria control measures

- Long-lasting insecticidal nets (LLIN)
  Supported by multiple RCTs to reduce all-cause mortality
- Indoor Residual Spraying with insecticide
- Various modalities for use of drugs as prevention
  SMC (children)
  iPTi (infants)
  iPTp (pregnant women)
- Rapid Diagnostic Tests to allow targeting of drugs
- Artemisinin Combination Treatments

All preventive and treatment measures suffer from the risk of drug and insecticide resistance
Malaria Vaccine Technology Roadmap
Launched in 2006 with Vision, Strategic Goal, and 11 Priority Areas

New Vision in 2013:
“Safe and effective vaccines against Plasmodium falciparum and Plasmodium vivax that prevent disease and death, and prevent transmission to enable malaria eradication.”
- Includes 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
- Speaks to the new emphasis on elimination and eradication

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.
Malaria Vaccine Technology Roadmap

Priority Areas

1. Research:
   - Confirm new candidates, to include using CHMI (controlled infections)
   - NEW-- Facilitate prompt reporting of human/NHP studies

2. Vaccine development:
   - Prioritize candidates using PPC; immune correlates; head to head testing
   - NEW-- Develop immune correlates and surrogates

3. Key capacities:
   - NEW– Ensure structures for pharmacovigilance and effectiveness

4. Policy & commercialization:
   - NEW– Encourage stewardship and support for vaccine development: project management; investment strategies; “making the business case”

Source: Salim Abdullah, 2014 report to WHO
Targeting the Parasite Life Cycle with Vaccines

- **Sporozoites**
  - Pre-erythrocytic (PE) Liver Stage (Anti-Infection Vaccines)

- **Interrupt Malaria Transmission (VIMT)**
  - Whole Organism Vaccine

  - **Mosquito Sexual Stage** (Transmission-Blocking Vaccines)

  - PE Subunit Vaccine

  - Transmission Blocking Vaccine

- **Asexual Blood Stage** (Anti-Disease Vaccines)
  - Clinical Malaria
  - Placental Malaria (PMV)
  - Severe Malaria (SMV)
Global malaria vaccine pipeline

**TRANSLATIONAL PROJECTS**

**Phase 1a**
- ChAd63/MVA ME-TRAP + Matrix M™
- Polyepitope DNA EP 1300
- PfCeITOS FMP012
- CSVAC
- ChAd63.AMA1/MVA.AMA1 +Al/CPG7909
- SR11.1
- ChAd63/MVA PvDBP

**Phase 2a**
- Ad35.CS/RTS,S-AS01
- Ad35.CS/Ad26.CS
- ChAd63/MVA (CS, TRAP, AMA)
- ChAd63.AMA1/MVA.AMA1
- FMP2.1-AS01B (AMA1 3D7)

**Phase 1b**
- M3V.Am.PfCA
- M3V.D/Ad.PfCA
- ChAd63/MVA MSP 1
- ChAd63.AMA1/MVA.AMA1
- EBA 175.R2

**Phase 2b**
- Ad35.CS
- ChAd63/MVA ME-TRAP
- SE36
- ChAd63.AMA1/MVA.AMA1
- GMZ2
- MSP3 [181-276]
- PfsPZ

**Phase 3**
- RTS,S-AS01

**VACCINE CANDIDATES**

**P. falciparum vaccines:**
- Pre-erythrocytic: ChAd63/MVA ME-TRAP, ChAd63.AMA1/MVA.AMA1
- Blood-stage: Ad35.CS, SE36, GMZ2, MSP3 [181-276], PfsPZ
- Transmission-blocking: RTS,S-AS01

**P. vivax vaccines:**
- Pre-erythrocytic: Pfs25-EPA, Pfs25-VLP

RTSS/AS01 Vaccine
Mosquirix®
In 2009, phase 3 trial of RTS,S/AS01 launched
- 11 research centers
- 7 countries
- various patterns of malaria transmission
- Partnership between GSK, MVI-PATH, and BMGF

The study population included
- children aged 5-17 months at first experimental immunization
- infants first immunized at 6-12 weeks of age together with EPI vaccines
RTSS/AS01 (Mosquirix®) Phase 3 results

• Initial efficacy estimates after 3 dose regimen against clinical malaria (fever; Pf > 5K/ul)
  In 6000 children: 50.4% (95%CI 45.8-54.6)
  In 6537 infants: 30.1% (95%CI 23.6, 36.1)

  Efficacy over 14 months after dose 1

• Analyses of phase 2 and 3 studies suggested waning of efficacy over 6 month windows
  In children: 68% (95%CI 64-72%), 41% (95%CI 36-46) and 26% (95%CI 19-33)
  In infants: 47% (95%CI 39-54), 23% (95%CI 15-31) and 12% (95%CI 1-21)

• Justified a study of giving a booster dose at month 20

RTSS/AS01 (Mosquirix®) Phase 3 results

• Results without a booster dose
  Children over mean 48 months followup:
  Protection against clinical malaria 28 % (95%CI 23-33)
  No protection against severe malaria
  negative efficacy -41.0% (95%CI −98.5 to −0.8) Month 21 to study end
  Infants over mean 38 months followup:
  Protection against clinical malaria 18 % (95%CI 12-24)
  No protection against severe malaria

• Results with a booster dose
  Children: Protection against clinical malaria 36 % (95%CI 32 to 41)
  Children: Protection against severe malaria 32 % (95%CI 14 to 47)
  Infants: Protection against clinical malaria 26 % (95%CI 20-32)
  Infants: No protection against severe malaria
  Infants: Reduced malaria hospitalizations 25% (95%CI 6-40)

The RTS,S/AS01 candidate vaccine received a positive scientific opinion from the European Medicine Agency (EMA) in July 2015.

Reviewed under article 58, which allows the EMA to give a scientific opinion about products exclusively for markets outside of the European Union.

World Health Organization will issue their position related to recommendations for use later this year.

Submission for review by national regulatory authorities in sub-Saharan African countries would follow.
Other Rainbow Table advanced candidates: ChAd63/MVA ME-TRAP; MSP3 (181-286)
ChAd63/MVA
ME-TRAP and CSP tested by CHMI

ChAd63/MVA ME-TRAP Protection against PCR+ in Kenyan adults

A Rainfall (mm/wk) and timing of interventions

B Any PCR positive *

11/61 (18%) ME-TRAP

28/60 (47%) rabies control

C >10 parasites/ml *

D PCR positive and new genotype *

MSP3-LSP/Aluminum Hydroxide safety trial

Clinical malaria: 37.5°C or higher; Pf density of 5000 parasites per microliter or more.
Risk period: 4 weeks after dose 3 until the end of the transmission season.
Sample size: N=15 children in each group; 12-24 months; Burkina Faso

Sirima et al NEJM 2011
PfSPZ Vaccine®
An Attenuated Whole Organism Vaccine
## INITIAL RESULTS (VRC 312)

*(Short Term Protection)*

CHMI 3 Weeks Post Last Dose - PfNF54 or Pf3D7 by Mosquito Bite

<table>
<thead>
<tr>
<th>Dosage Regimen</th>
<th>Anti-PfCSP Titer, Pre-CHMI (GM OD 1.0)</th>
<th>No. Protected/No. Challenged</th>
<th>Protective Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PfSPZ/Dose</td>
<td>Max. Total No. PfSPZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.5x10³</td>
<td>4 or 6</td>
<td>0.45x10⁵</td>
<td>13</td>
</tr>
<tr>
<td>3.0x10⁴</td>
<td>4 or 6</td>
<td>1.8x10⁵</td>
<td>324</td>
</tr>
<tr>
<td>1.35x10⁵</td>
<td>4</td>
<td>5.4x10⁵</td>
<td>3454</td>
</tr>
<tr>
<td>1.35x10⁵</td>
<td>5</td>
<td>6.75x10⁵</td>
<td>6716</td>
</tr>
</tbody>
</table>

*5/6 controls developed parasitemia*
# INITIAL RESULTS (VRC 312)

**(Durable Protection)**

<table>
<thead>
<tr>
<th>Dosage Regimen</th>
<th>No. of Doses</th>
<th>Total No. PfSPZ</th>
<th>No. Protected/ No. Challenged</th>
<th>Percent Protected</th>
</tr>
</thead>
<tbody>
<tr>
<td>PfSPZ/Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.35x10^5</td>
<td>4</td>
<td>5.4x10^5</td>
<td>1/3</td>
<td>33%</td>
</tr>
<tr>
<td>1.35x10^5</td>
<td>5</td>
<td>6.75x10^5</td>
<td>1/3</td>
<td>33%</td>
</tr>
</tbody>
</table>

CHMI 20 Weeks Post Last Dose - Pf3D7 by Mosquito Bite
PfSPZ Vaccine in Mali

- LN2 transport
- Sterile preparation
- Direct venous inoculation
Mali Trial Findings

- Repeated Direct Venous Inoculation of PfSPZ Vaccine® is:
  - Implementable in African Adults
  - Safe
  - Well tolerated

- PfSPZ Vaccine® is protective from infection in a region of intense transmission

- CSP ELISA responses are low in Malian exposed adults
  - very different from U.S. malaria naïve adults
  - CSP antibody responses may not be responsible for protection from infection
Next PfSPZ Vaccine® Trial in Mali: Dose Escalation, CHMI Efficacy (2015)
Sanaria, Inc. Next Steps

- Further optimization of immunization regimen for adults
  - Assessment in pregnancy and in HIV positive individuals

- Optimization of immunization in infants and children

- Determination if PfSPZ Vaccine protects against *P. vivax*

- Operational/implementation research
Transmission Blocking Vaccine Trial
Pfs25H-EPA/Alhydrogel
Thiolated Pfs25
Thiols/Pfs25 = 2-3

Maleimide-modified EPA
Maleimides/EPA = 6-9

Protein-Protein Conjugates form Nanoparticles

Conjugation
Pfs25:EPA=3:1 ratio
Thiols:Maleimides≈1:1

Dave Jones
Antibody Function After Pfs25-EPA/Alhydrogel in Mali

SMFA = Standard Membrane Feeding Assay
Measuring Vaccine Activity by “Mosquito Challenge” Studies: Direct Skin Feeds (DSF)

Results from 2014 Pfs25-EPA trial
- DSF on 79 volunteers weekly for 6 weeks
- Performed 459 DSF
- 15 positive DSF in 11 unique individuals
- Analyze “transmitters” vs “non-transmitters”
- Low power to detect highly active vaccine

Improve DSF power in future trials
- Increase sample size (N=200)
- 2 DSF per week on participants
- Analyze risk of infection per mosquito
- >90% power to detect vaccine activity 60%
Next TBV Field Trial: Pfs25-EPA + Pfs230-EPA / Alhydrogel

In-life toxicology study in rabbits ended without any safety concern

- Accelerated study design to move to the field
- US Phase 1: 1st dose in Jan 2015
- Mali Phase 1: 1st dose in Apr 2015
  - 4 dose, 2 year trial
- Vaccine activity: Fall 2016

- Future vaccine: Pfs25-EPA + Pfs230-EPA / AS01E
  - PoC trial for TBV concept
- Vaccine activity: Fall 2017
Malaria Vaccine Development Future Directions
Future Directions

- Preerythrocytic vaccines
  - PfSPZ Vaccine®
  - Improved CSP immunogens
  - Heterologous prime-boost regimens

- Transmission blocking vaccines
  - Proof of concept testing in field
  - Nanoparticles; Adjuvants; Platforms
  - Partner with CSP

- New Blood stage concepts: PfRH5; AMA1-RON2 complex

- Placental malaria vaccines will move to the field (EVI; NIAID)

- *P. vivax* is under-resourced
Ongoing WHO Roles

1. Facilitating interactions between group of major R&D funders
   • “Malaria vaccine funders group”
   • Identify gaps and reduce unhelpful overlaps
2. Finalizing preferred product characteristics
   • Provide details on desired profile of vaccines to meet 2 Strategic Goals
3. Maintaining 2x year updates for global portfolio
   • Rainbow Table
4. Engage in development of trial designs/assays for second generation vaccines
   • Transmission blocking vaccines
   • Studies using Controlled Human Malaria Infections (CHMI)

Source: Salim Abdullah, 2014 report to WHO
Acknowledgments

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