SKIN STAGE VIDEOS

1 Hour: IgG

6 Days: CD8

7 Days: IgG

1 Hour: IgG

Passive: IgG

NATURAL IMMUNITY IS STAGE-SPECIFIC
NATURALLY ACQUIRED IMMUNITY: SLOW TO DEVELOP, INCOMPLETE, AND OF LIMITED DURATION

Vaccine must do better

Parasite Immunology, 2006, 28, 51-60 Marsh & Kinyanjui

Despite 42% reduction since 2000, a child dies every minute in Africa from malaria

Three biggest risks:
- Financing fragility
- Artemisinin resistance
- Insecticide resistance

WHO World Malaria Report 2013

207 million malaria cases in 2012, 79% in Africa
627,000 deaths in 2012, 90% in Africa

207,000,000 malaria cases in 2012, 79% in Africa
627,000 deaths in 2012, 90% in Africa

Areas where malaria transmission occurs
Areas with high transmission
Areas with low transmission
**Clinical Malaria Vaccine Pipeline**

<table>
<thead>
<tr>
<th>Phase 1a</th>
<th>Phase 1b</th>
<th>Phase 2a</th>
<th>Phase 2b</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PfSPZ</td>
<td>PfSPZ</td>
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<tr>
<td>ChAd3</td>
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<tr>
<td>MVA</td>
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<tr>
<td>ME-TRAP</td>
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<td>ME-TRAP</td>
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<td>ME-TRAP</td>
</tr>
<tr>
<td>RTS,S/AS01</td>
<td>RTS,S/AS01</td>
<td>RTS,S/AS01</td>
<td>RTS,S/AS01</td>
<td>RTS,S/AS01</td>
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<tr>
<td>GMZ2</td>
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</tbody>
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**Most malaria vaccines are *P. falciparum* subunit vaccines**

- One mosquito antigen
- Few *P. vivax* antigens

- **Pfs25**
- **AgAPf1**
- **Pfs30**
- **Pfs25/Pfs30**

- **Antibodies**
- **Effector T cells**

- **Antibodies**: ≤5
- **Effector T cells**: ≤5
- **Antigens**: PfPy CSP, TRAP, LSA1, LSA3, CSU03

- **Pfs1**: AMA1, MSP3, GLURP, APAF1, MSP2, MSP1, AMA3, Pfs230, Pf48/45, Pfs25
Global Malaria Vaccine Portfolio by Platform

Total 45 projects in advanced pre-clinical & clinical

Source: WHO Rainbow Table Dec 2012:

Controlled Human Malaria Infection Model:
Biggest advantage for malaria vaccine development

Major responsibility to safeguard volunteer safety
Enhance comparability

RTS, S / AS01 Malaria Vaccine
GSK Biologicals/PATH MVI/BMGF

Repeats T epitopes S antigen
(from CS protein) (from HBV)

RTS & S co-expressed in Saccharomyces cerevisiae
RTS, S VLP

Malaria-Hep BsAg fusion VLP
Lyophilised
Point-of-use reconstitution with AS01 adjuvant: liposomes, MPL, QS21
**Key Phase 3 efficacy and immunogenicity results: 5-17 months and 6-12 weeks age categories**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>SVC (with 95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5-17 mo</td>
</tr>
<tr>
<td>First episode clinical malaria (ATP, adjusted, co-primary endpoint) (ITT, unadjusted)</td>
<td>55.8% (95%CI: 50.6; 60.4)</td>
</tr>
<tr>
<td>All clinical malaria episodes (ATP, adjusted) (ITT, unadjusted)</td>
<td>55.1% (95%CI: 50.0; 60.2)</td>
</tr>
<tr>
<td>Severe malaria (ATP) (ITT)</td>
<td>47.3% (95%CI: 42.2; 52.4)</td>
</tr>
<tr>
<td>Anti-CS antibodies GMTs (EU/mL)</td>
<td>621.2 (95%CI: 591.7; 652.1)</td>
</tr>
</tbody>
</table>

**Vaccine efficacy against clinical malaria over 18 months (8923 children 5-17 months and 6537 infants 6-12 weeks)**

<table>
<thead>
<tr>
<th>Time since vaccination</th>
<th>SVC children [95%CI]</th>
<th>SVC infants [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 months</td>
<td>68% [64 to 72]</td>
<td>47% [39 to 54]</td>
</tr>
<tr>
<td>0-12 months</td>
<td>51% [47 to 55]</td>
<td>33% [26 to 39]</td>
</tr>
<tr>
<td>0-18 months</td>
<td>46% [42 to 50]</td>
<td>27% [20 to 32]</td>
</tr>
</tbody>
</table>

**Comparative incidence of clinical malaria over 18 months (8923 children 5-17 months and 6537 infants 6-12 weeks)**

<table>
<thead>
<tr>
<th>Time since vaccination</th>
<th>Comparative incidence in children [95%CI]</th>
<th>Comparative incidence in infants [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 months</td>
<td>68% [64 to 72]</td>
<td>47% [39 to 54]</td>
</tr>
<tr>
<td>6-12 months</td>
<td>41% [36 to 46]</td>
<td>23% [15 to 31]</td>
</tr>
<tr>
<td>12-18 months</td>
<td>26% [19 to 33]</td>
<td>12% [1 to 21]</td>
</tr>
</tbody>
</table>
Vaccine efficacy over 18 mo by site – all episodes of clinical malaria

Children 5-17 months

Infants 6-12 weeks

• No clear variation in efficacy according to transmission level.
• Benefit of the vaccine (episodes prevented) likely to be greatest in high transmission settings.
• 3-fold higher immunogenicity for anti-CS IgG in older age group.
• Immunological immaturity?
• Interference from maternal antibodies?
• Interference from co-administration with other vaccines?

Immunological basis of efficacy?

- Very high titre IgG to conserved sporozoite surface antigenic component is most strongly associated with protection against infection.

Further reading
White NF et al. PLoS ONE April 2013
Moorthy VS & Ballou WR. Malaria J 2009, 8:312

Other Pre-erythrocytic Vaccines

US Navy/Genvec DNA/Ad5 prime-boost CS/AMA1
Oxford/Okairos AdCh63/MVA ME-TRAP*

Both confirm promise of adenovirus vectors for CD8 in humans when used in prime-boost combinations
Both led to about 20% protection in challenge trials

§ Poster Presented at Keystone conference 2010
* Hill AV et al. Human Vaccines 2010 Jan;6(1):78-83
Many Blood stage vaccines are under evaluation

Blood-stage vaccines: scientific challenges

Key issues:
- Will strain-transcending protection be possible?
  - See AMA1 NEJM paper
  - Polyvalent vs conserved regions
- Can challenge trials be used to accelerate blood stage vaccine development?
- Can newly identified antigens be promptly transitioned into vaccine development?

LETTER RESEARCH HIGHLIGHT: New Ag

Basigin is a receptor essential for erythrocyte invasion by Plasmodium falciparum

First essential red cell receptor for P.falciparum recently identified as Basigin

Rh5 is the ligand, and anti-Rh5 IgG induce strain-transcending functional activity
Sexual stage/mosquito antigen vaccines are conceptually attractive for interrupting transmission.

Antibodies

- Pfs25
- Pfs230
- Pf25

Effector T cells

- PfPv CSP
- TRAP
- LSA1
- LSA3
- CED15

Standard Membrane Feeding Assay (SMFA): functional activity of IgG to sexual stage/mosquito antigens

In vitro cultured gametocytes are source of parasites.

Test serum (IgG) and control serum (IgG) are compared.

Blood containing gametocytes + test pesticide

Jacket for warm water

Artificial or Natural Membrane

Stained mosquito gut 6 days post feed

Schizont

Midgut
**P. vivax**

- If Pf disease burdens drop, Pv will increase in R&D priority
- *P. vivax* human challenge model being strengthened (...some difficulties with relapse, lack of Pv culture)
- First *P. vivax* challenge trial has occurred with a *P. vivax* CS recombinant protein in AS01
- Clinical evaluation of *P. vivax* vaccines may pose challenges (interactions with Pf, distinguishing new infections from hypnozoite reactivation)

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**Take home messages**

- There is no licensed or available malaria vaccine
- One candidate RTS,S/AS01 is the most advanced, and the first WHO recommendations on use are expected in late 2015
- Even higher efficacy vaccines are desired and we have 2030 goals for highly effective clinical disease prevention and elimination vaccines
- Non-vaccine control ↓deaths by 42% to estimated 627,000 over last decade. Emerging drug and insecticide resistance threaten malaria control. New tools are needed.
- Malaria Vaccine R&D is a very active and exciting area!

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**Thank you!**

- For further info on malaria vaccine R&D see WHO IVR website
  - [www.who.int/vaccine_research](http://www.who.int/vaccine_research)
  - [www.who.int/vaccine_research/Malaria/en/index.html](http://www.who.int/vaccine_research/Malaria/en/index.html)
  - or email moorthyv@who.int

- For info on malaria policy, status of malaria control/elimination, see WHO Global Malaria Programme
  - [www.who.int/malaria](http://www.who.int/malaria)