Progress and Challenges in Malaria Vaccines

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SKIN STAGE VIDEOS

1 Hour: IgG
1 Hour: IgG

6 Days: CD8

7 Days: 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
The burden of malaria caused by *Plasmodium falciparum*

- 219 million malaria cases in 2010, 79% in Africa
- 660,000 deaths in 2010, 90% in Africa
- Mostly children under 5 years (86%)
- Cost $12 billion and loss of 1.3% of economic growth annually in Africa
2013 Update

- 99 malaria-endemic countries in 2010
- Deaths *estimated* at 660,000 per year for 2010 (range 490,000 to 836,000)
- Uncertainty range highlights need to strengthen surveillance: major focus
- 219 million cases *estimated* for 2010
- Early artemisinin drug resistance detected in south-east Asia
# Clinical malaria vaccine pipeline April 2013

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<th>Phase 1a</th>
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**P. falciparum vaccines:**
- Pre-erythrocytic
- Blood-stage
- Transmission-blocking

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

Most malaria vaccines are subunit vaccines

Pvs25/Pfs25
AgAPN1
Pfs230
Pfs48/45

<5

<50

Pf, Pv CSP
TRAP
LSA1
LSA3
CELTOS

MSP1
AMA1
MSP3
GLURP, SERA,
SR11.1, P27, MSP2,
EBA175, PvDBP, Rh

~100,000,000,000

Antibodies

Effector T cells

Antibodies
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:

Major responsibility to safeguard volunteer safety

Enhance comparability
Efficacy trials of malaria vaccines: Hierarchy of endpoints

- Early field trials (n=300-1000)
  - Blood stage infection
  - Clinical malaria
  - Severe malaria
  - Death

- Challenge trials (n=20-100)

- Late field trials (n=2000-20000)
Pre-erythrocytic Vaccines

Antibodies
- Pvs25/Pfs25
- AgAPN1
- Pfs230
- Pfs48/45

<5

Effector T cells
- Pf Pv CSP
- TRAP
- LSA1
- LSA3
- CELTOS

~100,000,000,000

Antibodies
- MSP1
- AMA1
- MSP3
- GLURP, SERA, SR11.1, P27, MSP2, EBA175, PvDBP, Rh

<50
Repeats T epitopes
(from CS protein)

S antigen
(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
Phase 3 multi-centre efficacy trial

11 participating centres in 7 African countries

Depending on the full results to become available in 2014, and on the regulatory submission timings, WHO policy recommendations are expected in Q4 2015.
Phase 3 Trial Study design

- Designed to provide both data for filing and to support assessment of public health impact for possible implementation

- 15,460 children in 2 age categories:
  - 6 to 12 weeks in co-administration with infant vaccines
  - 5 to 17 months
  - 0,1, 2 month schedule

- 1:1:1 randomisation to include an arm with booster immunization at 18 months

- Total trial duration per child 30 months

Hum Vaccin. 2010 Jan;6(1):90-6
# Key Phase 3 efficacy and immunogenicity results: 5-17 months and 6-12 weeks age categories

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<tr>
<th>Endpoint</th>
<th>%VE (with 95%CI)</th>
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<tr>
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<td>5-17 mo</td>
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<tr>
<td><strong>First episode clinical malaria</strong></td>
<td></td>
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<tr>
<td>(ATP, adjusted, co-primary endpoint)</td>
<td>55.8% (97.5%CI: 50.6; 60.4)</td>
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<tr>
<td>(ITT, unadjusted)</td>
<td>50.4% (45.8; 54.6)</td>
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<td><strong>All clinical malaria episodes</strong></td>
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<tr>
<td>(ATP, adjusted)</td>
<td>55.1% (50.5; 59.2)</td>
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<tr>
<td>(ITT, unadjusted)</td>
<td>53.9% (49.6; 57.8)</td>
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<td><strong>Severe malaria</strong></td>
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<tr>
<td>(ATP)</td>
<td>47.3% (22.4; 64.2)</td>
</tr>
<tr>
<td>(ITT)</td>
<td>45.1% (23.8; 60.5)</td>
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<tr>
<td><strong>Anti-CS antibodies GMTs (EU/mL)</strong></td>
<td>621.2 (591.7-652.1)</td>
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ATP: According to protocol  
ITT: Intent to treat  
CI: Confidence Intervals  
GMT: Geometric Mean Titers

*NEJM 2011; 365: 1863-1875*  
*NEJM 2012; 367: 2284-95*
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 MT 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

Pvs25 /Pfs25
AgAPN1
Pfs230
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Antibodies
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**Blood stage vaccines dominate phase 1-2 field status**

Two large projects with 800-1200 subjects enrolled in Africa

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*P. falciparum* vaccines:  

- Pre-erythrocytic  
- Blood-stage  
- Transmission-blocking

*P. vivax* vaccines:  

- Pre-erythrocytic  
- Blood-stage  
- Transmission-blocking

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?
Basigin is a receptor essential for erythrocyte invasion by *Plasmodium falciparum*

Cécile Crosnier\(^1\)*, Leyla Y. Bustamante\(^2\)*, S. Josefin Bartholdson\(^1\)*, Amy K. Bei\(^3\), Michel Theron\(^2\), Makoto Uchikawa\(^4\), Souleymane Mboup\(^5\), Omar Ndir\(^5\), Dominic P. Kwiatkowski\(^2,6\), Manoj T. Duraisingh\(^3\), Julian C. Rayner\(^2\) & Gavin J. Wright\(^1,2\)

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
Malaria transmission blocking vaccines: an ideal public good
Sexual stage/mosquito antigen vaccines are conceptually attractive for interrupting transmission

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- Antibodies

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Antibodies
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
**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).
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 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 25% to estimated 660,000 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!
Thank you!

- For further info on malaria vaccine R&D see WHO IVR website
  - www.who.int/vaccine_research
  - 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