Progress and Challenges in Malaria Vaccines

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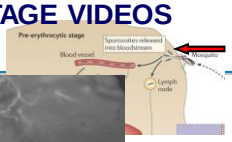
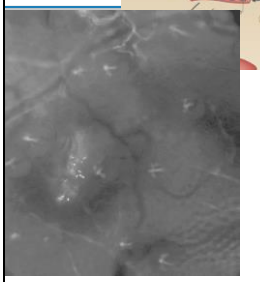
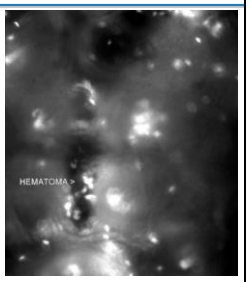
World Health Organization

SKIN STAGE VIDEOS



1 Hour: IgG





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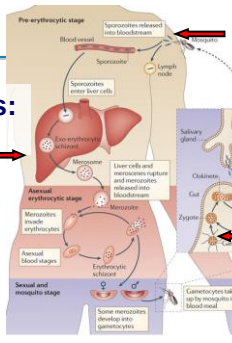

1 Hour: IgG

6 Days: CD8

7 Days: IgG

Passive: IgG

NATURAL IMMUNITY IS STAGE-SPECIFIC

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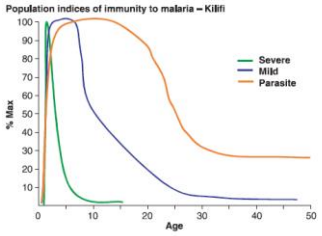
NATURALLY ACQUIRED IMMUNITY: SLOW TO DEVELOP, INCOMPLETE, AND OF LIMITED DURATION

Vaccine must do better



Parasite Immunology, 2006, **28**, 51–60 Marsh & Kinyanjui

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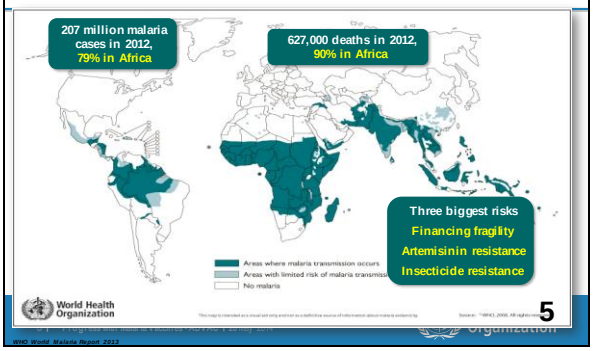
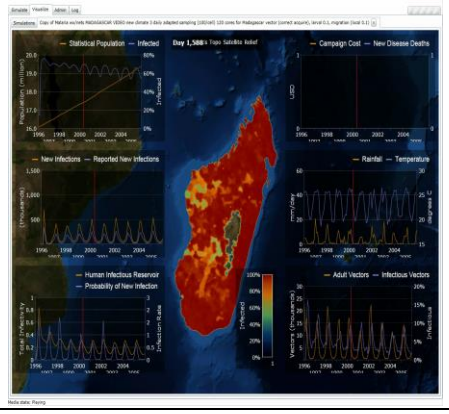
Despite 42% reduction since 2000, a child dies every minute in Africa from malaria

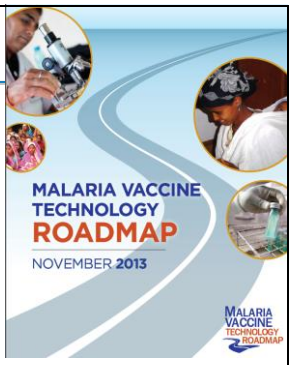




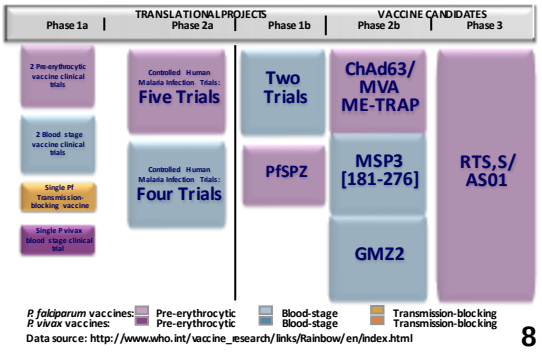
2 Strategic Goals:
Public health needs to be met by vaccination

13 Priority R&D Areas

Global Funders Group for coordination



Clinical Malaria Vaccine Pipeline



Data source: http://www.who.int/vaccine_research/links/Rainbow/en/index.html

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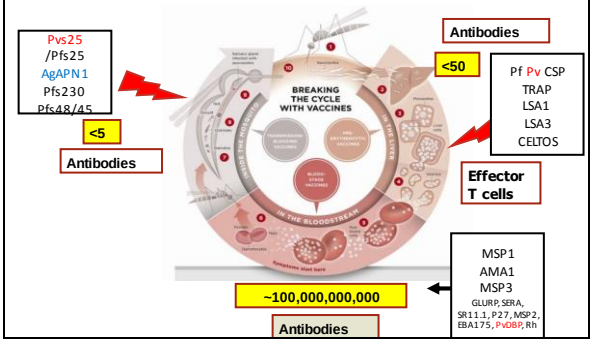
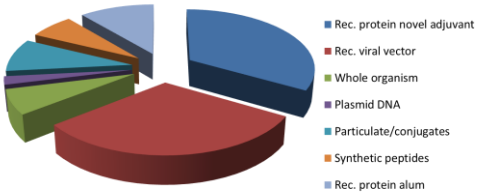
Most malaria vaccines are *P. falciparum* subunit vaccines

One mosquito antigen
Few *P. vivax* antigens



Global Malaria Vaccine Portfolio by Platform

Total 45 projects in advanced pre-clinical & clinical



Source WHO Rainbow Table Dec 2012:
www.who.int/vaccine_research/links/Rainbow/en/index.html

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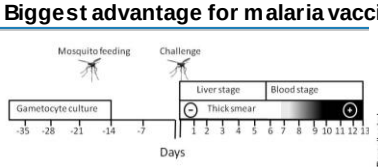
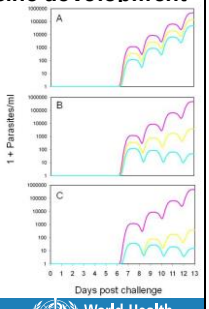
Controlled Human Malaria Infection Model: Biggest advantage for malaria vaccine development





Major responsibility to safeguard volunteer safety

Enhance comparability

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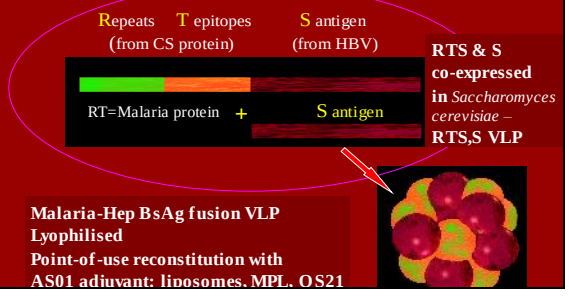
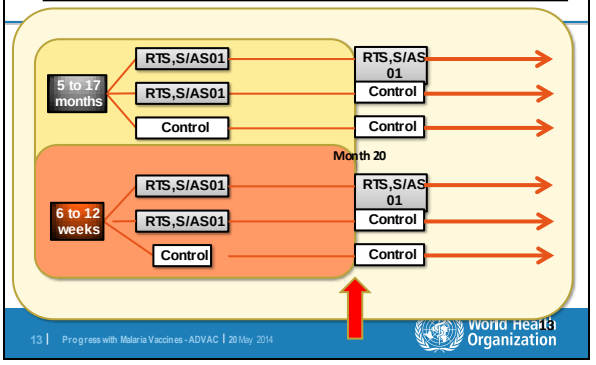
RTS,S / AS01 Malaria Vaccine
GSK Biologicals/PATH MVI/BMGF



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

Design of RTS,S/AS01 Trial



Key Phase 3 efficacy and immunogenicity results: 5-17 months and 6-12 weeks age categories

Endpoint	%VE (with 95%CI)	
	5-17 mo	6-12 wk
First episode clinical malaria (ATP, adjusted, co-primary endpoint) (ITT, unadjusted)	**55.8%** (97.5%CI:50.6;60.4) **50.4%** (45.8;54.6)	**31.3%** (97.5%CI:23.6;38.3) **30.1%** (23.6;36.1)
All clinical malaria episodes (ATP, adjusted) (ITT, unadjusted)	**55.1%** (50.5;59.2) **53.9%** (49.6;57.8)	**33.0%** (26.4;38.9) **32.9%** (26.7;38.5)
Severe malaria (ATP) (ITT)	**47.3%** (22.4;64.2) **45.1%** (23.8;60.5)	**36.6%** (4.6;57.7) **26.0%** (-7.4;48.6)
Anti-CS antibodies GMTs (EU/mL)	**621.2** (591.7-652.1)	**209.2** (196.8-222.4)
	NEJM 2011;365:1863-1875	*NEJM 2012;367:2284-95*

ATP: According to protocol
ITT: Intent to treat
CI: Confidence Intervals
GMT: Geometric Mean Titers

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

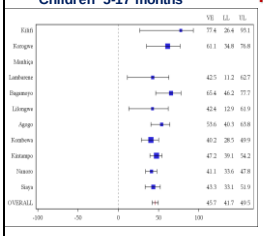
Time since vaccination	VE in children [95%CI]	VE in infants [95%CI]
0-6 months	**68%** [64 to 72]	**47%** [39 to 54]
0-12 months	**51%** [47 to 55]	**33%** [26 - 39]
0-18 months	**46%** [42 to 50]	**27%** [20 – 32]

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

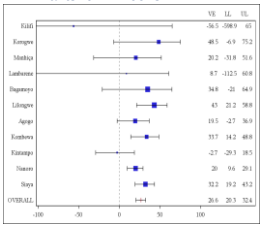
Time since vaccination	Comparative incidence in children [95%CI]	Comparative incidence in infants [95%CI]
0-6 months	**68%** [64 to 72]	**47%** [39 to 54]
6-12 months	**41%** [36 to 46]	**23%** [15 to 31]
12-18 months	**26%** [19 to 33]	**12%** [1 to 21]

Vaccine efficacy over 18 mo by site – all episodes of clinical malaria

Children 5-17 months

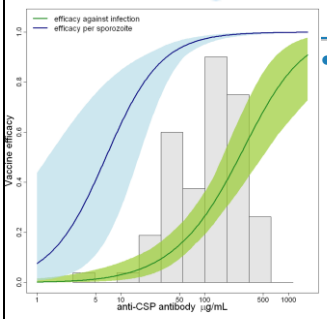


Infants 6-12 weeks



- 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 MT et al. PLoS ONE April 2013
Moorthy VS & Ballou WR. Malaria J 2009, 8:312

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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

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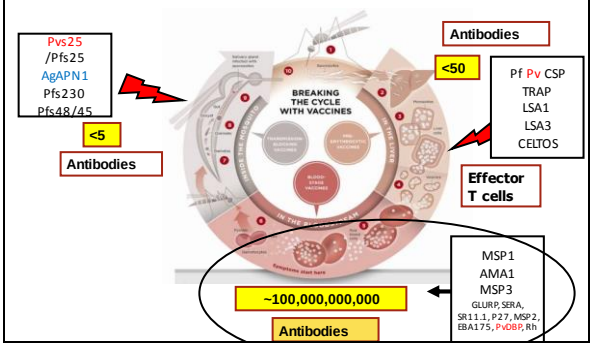
Many Blood stage vaccines are under evaluation



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?

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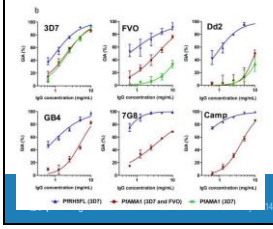
LETTER **RESEARCH HIGHLIGHT: New Ag**

doi:10.1038/nature1064

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

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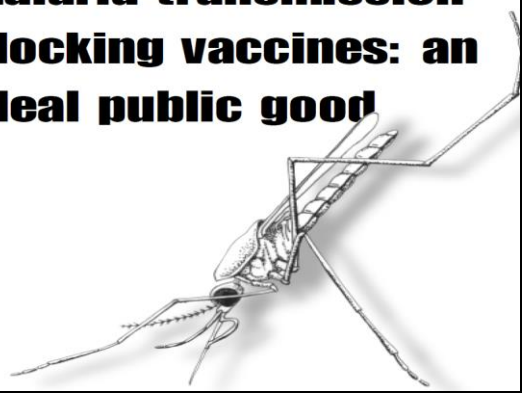
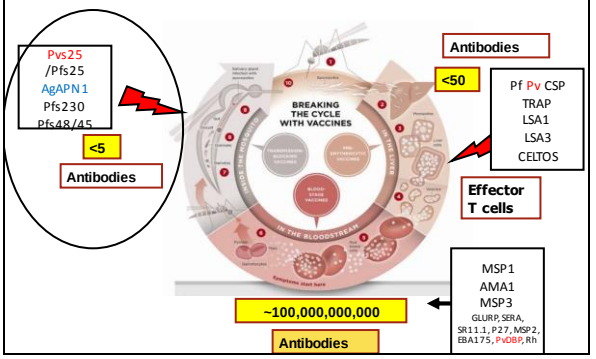
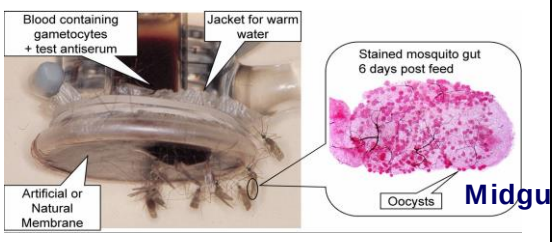
Malaria transmission blocking vaccines: an ideal public good



Sexual stage/mosquito antigen vaccines are conceptually attractive for interrupting transmission



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 drops, 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 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!

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