Malaria Vaccines: Scientific overview of the field

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Malaria vaccine design: Points for intervention
Sporozoites – liver stage – blood stage

From injection of sporozoites to start of blood stage takes 6 days for *P. falciparum*

1 sporozoite leads to about 30,000 merozoites leaving liver
<table>
<thead>
<tr>
<th>Target stage</th>
<th>Clinical effect</th>
<th>Antigens</th>
<th>Possible Immune mechanism</th>
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<tbody>
<tr>
<td></td>
<td>Prevent infection and disease</td>
<td>CSP, TRAP, LSA1, LSA3</td>
<td>Humoral</td>
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<td>Reduce clinical disease severity</td>
<td>MSP1, MSP2, AMA1, MSP3, GLURP, SERA</td>
<td>Cell-Mediated</td>
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<td>Interrupt transmission</td>
<td>PvsS25, PfS25</td>
<td>Humoral</td>
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Main development approaches
- Subunit vaccines; > 60% of candidates are recombinant proteins
- Recombinant viral vectored vaccines

Other approaches
- Long synthetic peptides
- DNA vaccines
- Whole parasite vaccines
  - sporozoites attenuated by irradiation or by gene deletion
Antigen Discovery/Validation Systems

Antigen - localization; structure; function; lethality of gene knockout; polymorphism
Animal models - Immunogenicity; Protection against challenge
In vitro assays Immuno-epidemiological correlations Manufacturability

Public Health Impact
- Impact and interaction with other interventions
- Cost and effectiveness

Malaria Burden/Healthcare System Relationship

What are meaningful measures of vaccine efficacy?
- Infection, Clinical malaria, Severe Malaria, Anaemia, Death
- Parasite genotype, multiplicity of infection

What are relevant immune Responses?
- humoral
- cellular
- functional

Desirable Vaccine Product Profile

Vaccine Concept

Human Immune System

Plasmodium/Human host Interaction

World Health Organization
Current vaccine concepts: Selection and design strategies

- Identify 'key' targets of protective immune responses thought to be protective (from irradiated sporozoite model, animal models, clinical models)

- Design vaccines that maximally induce the hypothesized protective immune response
  - Choice of antigen
  - Need for multiple alleles?
  - Choice of expression system
  - Choice of platform/ adjuvant
  - Need for VLP for recombinant protein approaches?
Efficacy trials of malaria vaccines

- Early field trials
- Challenge Trials
- Late field trials

- Challenge
  - Blood Stage Infection
  - Clinical Malaria
  - Severe Malaria
- Death
Pre-erythrocytic candidate vaccines
RTS,S / AS01 Malaria Vaccine
GSK Biologicals/PATH MVI

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
RTS,S \((MVI/GSK)\)

GSK/MVI RTS,S/AS01 clinical development program: Multi-centre, Multi-country Phase 3 pivotal trial planned for 2009 start

Phase 2 field efficacy data with earlier adjuvant AS02

- 30% efficacy (95%CI 11-45%) against incidence rate of first episode of clinical malaria in Mozambique in 2,022 children aged 1-4

- 57% efficacy (95%CI 16-80%) against severe malaria

- Duration of efficacy demonstrated for 18 months with AS02

- Follow-up for 2 further years submitted for publication
Vaccine Efficacy – 18 months follow-up

VE: 35% (21.6%, 46.6%) p<0.0001

Double blind phase
Single blind phase

p <0.0001 (logrank test)
RTS,S (MVI/GSK)

Phase 2 field efficacy data with RTS,S/AS01 in 850 Kenyan and Tanzanian infants aged 5-17 months

- 56% efficacy – incidence rate of all episodes of malaria over 8 months

- 1 episode of severe malaria in RTS,S group vs 8 episodes in control group

- This protection occurred in a setting with reducing transmission intensity and 70% bednet use

- Efficacy against severe disease promising in phase 2 studies to date
Phase 3 Trial Study design

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

- Up to 16,000 children in 2 age categories:
  - 6 to 12 weeks in co-administration with EPI 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
Phase 3 multi-centre efficacy trial

11 participating centres in 7 African countries
**Immunological basis of efficacy?**

- No clear correlate of protection emerges from clinical trial data.
- There is a consistent relationship between higher CS repeat IgG levels and protection from infection in challenge and field trials.
- There is good data to indicate that cell-mediated responses have an additive role in addition to IgG for RTS,S.
- Key T cell responses in humans appear to be CD4+ effector T cell responses: CD8 responses are absent or weak after RTS,S immunization in humans.
- Protective mechanisms of both T cell and B cell immunogenicity to be further explored.
Immunological bases of efficacy?

- Association of IgG levels to CS protein with efficacy against morbidity was not seen in the Mozambique study with 2022 children aged 1-4.

- Associations between IgG levels and efficacy against infection have been seen in several trials in adult Americans, adult Gambians and infants in Mozambique.

- Understanding relationship between impact on infection and impact on clinical disease remains a work in progress.
FP9/MVA ME-TRAP (*Oxford/Oxxon*)

- Recombinant FP9 (fowlpox) boosted with Modified Vaccinia Ankara vector bearing multiple pre-erythrocytic epitopes and TRAP

- Multiple UK challenge trials with ME-TRAP
  - mean 40 hour extension in pre-patent period
  - High CD4+ T cell immunogenicity with DNA/MVA regime

*No efficacy against disease shown in recent Kenyan pediatric trial but immunogenicity was lower in paediatric population*
Immunological lessons?

- **What are the appropriate T cell assays for paediatric trials?** Assay development needed

- Immunogenicity in adults was not predictive of paediatric field setting with vectored vaccines – why?

- **Can T cell responses protect in the absence of antibodies?** *Never yet proven in human malaria*

- **Evidence that delay without complete protection in challenge trials does not correlate with field efficacy**
Other pre-erythrocytic vaccines

- Ad5-CS (Genvec) & Ad35-CS (Crucell) in phase 1 trials

- AdCh63/MVA ME-TRAP (Oxford) in phase 2a trials

- Liver-stage antigen LSA1/AS02 failed in Phase 2a (WRAIR/GSK)

- Liver-stage antigen LSA3 in clinical development (Institut Pasteur)
Blood-stage vaccines
Blood-stage vaccines: scientific challenges

- No known immune correlates of protection
- No clear positive signal in a clinical challenge trial with blood stage vaccines to date
- Little agreement on which assays are of utility for decision-making
- Efficacy read-out (clinical disease, severe disease) in the landscape of evolving immune status as age and exposure changes – complex, can mitigate results and interpretation in trials
Antigens in the pipeline

- MSP1 (Phase 2 Kenya – no efficacy)
- AMA1 (Phase 2 Mali - pending)
- MSP1-19/ AMA-1 combination (Phase 1 China)
- MSP3 (Phase 2 trial Mali - pending)
- GLURP/MSP3 combination (GMZ2 Phase 1 Gabon)
- MSP2 (Phase 1 Australia)
Transmission-blocking Vaccines
Vaccine rationale: prevent transmission

- Target antigens on gametes, zygotes, ookinetes or mosquito midgut

- Vaccine-induced antibody ingested with the gametocytes would block fertilisation in the mosquito midgut, and thus reduce malaria transmission and disease burden.

- Development facilitated by ability to measure transmission blocking activity in sera in a membrane feeding assay

- Could imperfect pre-erythrocytic and blood-stage vaccines also exert public health impact by reducing transmission of parasites?

- Major questions around clinical evaluation and regulatory pathways
Whole parasite approaches
Alternatives: Irradiated sporozoite vaccine by SANARIA

- Can one produce adequate quantities of sporozoites?
- Can one “practically” and reproducibly produce sporozoites that have the physical characteristics to allow them to meet regulatory, potency and safety requirements to be a vaccine?
- Can sporozoites be stored for extended periods of time at temperature higher than that of liquid nitrogen?
- Can one administer the attenuated sporozoites by a route that is practical for a vaccine?
- First phase 1 trial of vialled irradiated sporozoites planned to start late May 2009 under FDA IND
Malaria Vaccines Overview - ADVAC | 22 May 2009

Illustrative

- RTS,S/AS01 (GSK/MVI)
- RTS,S/AS02 (GSK/MVI)
- MSP1/AS02 (WRAIR/GSK)
- FP9/MVA ME-TRAP (Oxford)
- AMA1/AS02 (WRAIR/GSK)
- MSP3 (EMVI/AMANET)
- GMZ2 (EMVI/AMANET)
- AMA1 (BPRC)
- MSP1 FVO (WRAIR/GSK)
- SE36 (OSAKA)
- LSA1/AS01/AS02 (WRAIR)
- AMA1/AS02 (WRAIR/GSK)
- Virosomal (Pevion)
- Pfs25 (NIAID)
- EBA175 (NIAID)
- Ad35 CSP (NIAID)
- Ad5 CSP (NMRC)
- Ad63/MVA ME-TRAP (Oxford)
- γ Sporozoite (Sanaria)
- CP2.9 (Wanxing)
- MSP1 FVO

Pivotal Phase 3

Safety Infants

Paediatric efficacy

Paediatric safety

Challenge trial efficacy

Safety in semi-immunes

Safety in non-immunes

Ongoing trial activity in sub-Saharan Africa

2004 2005 2006 2007 2008 2009 2010

RTS,S/AS01

RTS,S/AS02

MSP1/AS02

FP9/MVA ME-TRAP

AMA1/AS02

MSP3

GMZ2

AMA1-C1/Alhydrogel

AMA1/AS02

Virosomal

Pfs25

SE36

LSA1/AS01/AS02

AMA1/AS02

Virosomal

Pfs25
Malaria Vaccine Global Pipeline

- Global Portfolio of candidate vaccines available at IVR website

http://www.who.int/vaccine_research/documents/Malaria_Vaccine_Rainbow_Table_Clinical_Oct_2008.pdf

http://www.who.int/vaccine_research/documents/Malaria%20Vaccine%20Rainbow%20Table_Preclinical_Oct_2008.pdf

- > 50% based on three antigens CSP, AMA1 and MSP 1

- About 16 candidates in active clinical development
Addressing critical research and development challenges
The Malaria Vaccine Roadmap

- 230 experts from 35 countries consulted in a series of meetings from 2004-2006
- Agreed of vision and goal of a malaria vaccine by 2025
- Global R&D strategy for a vaccine against falciparum malaria in African children
  - Research
  - Vaccine development
  - Key Capacities
  - Policy and Commercialization
Roadmap Priority Areas

- **Research**
  - Develop a standard set of immunological assays with standardized procedures and reagents to enable comparisons of the immune responses of vaccines
  - Standardize clinical trial design and assessment to compare data and to determine correlates of protection
  - Pursue rational antigen discovery through proper application of immunological knowledge and latest available tools
  - Develop web-based information-sharing tools to strengthen connections between the laboratory and the clinic

- **Vaccine Development**
  - Establish a systematic approach for prioritizing sub-unit vaccine candidates using accepted pre-clinical criteria
  - Pursue alternative strategies

- **Key Capacities**
  - Establish readily accessible formulation and scale-up process development capacity for malaria vaccines
  - Build and broaden capacity to accommodate the growing number of trials required for malaria vaccine development.

- **Policy and Commercialization**
  - Develop novel regulatory strategies to expedite approval while ensuring safety
  - Establish country-level dialogue to prepare and facilitate future policies on malaria vaccine introduction
  - Explore and develop sustainable financing options
Challenges with malaria vaccine efficacy analysis and interpretation

- Interpretation of clinical trial efficacy data is not intuitive – guidance is necessary for non-experts

- Genuine challenges remain in analysis eg approaches to analysis of multiple episodes of malaria, estimating duration of efficacy, analysis of \textit{P. vivax} efficacy in co-endemic areas

- Scientific, regulatory and public health perspectives all need to be taken into account
Beyond efficacy: what more do we need to know about the public health effects of vaccines?

- the potential effects of vaccines on malaria transmission
- limitations of what can be inferred from trials
- What mathematical models have to offer to estimate mid-to-long term impact in context of other control measures and against background of changing malaria epidemiology
Financing of malaria vaccines

- Are there epidemiological settings where imperfect vaccines would exert maximum public health impact?

- Which global fund would be the most suited? GAVI and/or the GFATM?

- Should there be an AMC for malaria vaccines?
The Involvement of the Bill and Melinda Gates Foundation in Vaccinology

ADVAC 9
Annecy, France 2009

W. Ripley Ballou, MD
Deputy Director, Vaccines
Infectious Diseases Development
Bill and Melinda Gates Foundation
A Family Foundation
- Number of employees: approximately 760
- Asset trust endowment: $27.5 billion
- Total grants since inception: $20.1 billion
- Total 2008 grant payments: $2.800 billion

Programs (% investment)
- Global Health (~50%)
- Global Development (~25%)
- US Programs (~25%)
Vaccines play a dominant role in our programs
Diseases and Conditions addressed by the Foundation

Total Global Health Burden (DALYs*)

- Noncommunicable conditions: 687,815,000
- Injuries: 181,991,000
- Communicable diseases not addressed by the foundation: 45,070,000

Diseases and conditions addressed by the foundation - 38% of the global health burden

- Acute lower respiratory infections: 91,374,000
- HIV/AIDS: 84,458,000
- Acute diarrheal illness: 61,966,000
- Vaccine-preventable diseases: 43,650,000
- Malaria: 46,486,000
- Tuberculosis: 34,736,000
- Malnutrition and undernutrition: 34,417,000
- Reproductive & maternal health: 33,632,000
- Child health: 97,335,000
- Other health conditions: 36,389,000

*Disability-Adjusted Life-Years Lost
Decision Process for Vaccine Investments

- What would be the potential impact?
- What is the desired Target Product Profile?
- How would the investment overcome the limitations of current options and available products?
- Would the intervention be cost-effective?
- Does it provide a possible permanent solution to a problem?
- What are the barriers to use and adoption?
- Are there potential secondary effects such as herd immunity?
Translation through a variety of grant models

- Not-for-profit PDPs that partner with industry
  - PATH, IAVI, MVI, AERAS
- Operational foundations that partner with academia
  - Sabin Vaccine Institute/GWU;
- Academic grantee that partners with biotech and industry
  - Oxford University/Emergent
- Grantees outside of the U.S.
  - FIND, MMV
- Direct grants to Industry in context of “global access strategy”
- Operating principles: respect for IP, GMP and GCP
GAVI Alliance: Bringing more vaccines to more people

- Estimated 2.6 million deaths prevented since 2000 – WHO, 2007
  » Immunizations in 2006 averted estimated 600,000 future deaths
- Coverage has improved
  » Hepatitis B vaccine coverage in GAVI-eligible countries: from 20% (2000) to 45% (2005)
  » 28 million more children have been protected against DTP – immunization rates increased from 63% (1999) to 77% (2006)
  » 138 million more children received new and under-used vaccines (Hib, yellow fever).
  » 1.2 billion auto-disable syringes delivered
  » Pneumococcal conjugates and Rotavirus vaccines... Soon!
Some Examples
Grand Challenges Programs

- Grand Challenge in Global Health (2003, $436M)
  » Needle-free delivery and vaccine stabilization strategies
  » Mucosal immunization delivery strategies
  » Novel mouse models to improve vaccine development
  » Biomarkers and correlates of immunity

- Grand Challenges Explorations (2008, $100M)
  » Create New Ways to Induce Mucosal Immunity
  » Create New Vaccines for Diarrhea, HIV, Malaria, Pneumonia and Tuberculosis
  » Create New Tools to Accelerate Malaria Eradication
The Collaboration for AIDS Vaccine Discovery

- An international network of scientists and experts dedicated to designing a variety of novel HIV vaccine candidates and advancing the most promising candidates to clinical trials.

- Operating Principles
  » Dedicated and creative scientific community
  » Accelerating progress toward an AIDS vaccine
  » Collaborative approach emphasizing
    • sharing of scientific information
    • standardization of laboratory techniques and data analysis.
Meningitis A Vaccine Project

Project Coordinated by WHO and PATH

- Supply and tech transfer of meningococcal polysaccharide A from Dutch partner (SynCo BioPartners B.V.)
- Serum Institute of India, Limited (SII) for tetanus toxoid and vaccine manufacturing
- US FDA for novel conjugation technology
- Phase 1 trials in India
- Phase 2 trials in 3 African sites
- Supply commitments (25M doses) at global access price
- Country plans for roll out of catch-up immunization
JE Vaccine Project
Live attenuated SA 14-14-2 JE vaccine

- Developed in China for domestic use
- Licensed in 1988, used in 200 million children in China
- File incomplete for international submission and EPI use
- Project started in 2003, PATH worked with China (Chengdu) producer to
  - conduct additional trials
  - increase production capacity (new facility)
  - technical support in licensing (India) and introduction
- 2007 ~35 million children vaccinated in India, Nepal and Sri Lanka
- India financed 5 year commitment as a national priority in midst of epidemic
Rotavirus Vaccine Program at PATH (ARVAC)

- Accelerate the introduction of safe, effective, and affordable rotavirus vaccines in developing countries.
- Provide targeted support and technical assistance to three developing country manufacturers: BBIL, Shantha, and WIBP.
- Share enabling platform in the network of NIH licensees.
## ARVAC portfolio: Stage of development

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<th>Leader</th>
<th>Partner</th>
<th>Product</th>
<th>Res</th>
<th>PreCl*</th>
<th>Ph 1</th>
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<th>Ph 3</th>
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*Pre-clinic, defined as in GMP Manufacturing, Tox, and RA*

- **2007**
- **3Q 2008**
- **Oct 2011, end of ARVAC grant**
IDRI Adjuvant Development Program

- Funded by the foundation to develop and make available to the research community a portfolio of potent, well characterized adjuvants
- Currently has nine malaria and six HIV collaborations, plus influenza subunit and leishmaniasis in portfolio of projects
- Has portfolio of more than 30 adjuvant formulations under evaluation including immunostimulants in aqueous solutions and adsorbed to alum, oil-in-water emulsions and liposomes with and without immunostimulants, and other novel concepts
- Industry-experienced development team works with collaborators to optimize adjuvant selection and formulation
- Active oversight with experts from industry, NIH, WHO/IVR and foundation
The MVI/GSK RTS,S Development Program

An affordable malaria vaccine for infants and young children in sub-Saharan Africa that

- will be safe and well tolerated
- will significantly reduce the number of clinical episodes and risk of severe malaria disease due to *P. falciparum*
- is implementable through existing delivery programs
  - EPI schedule(s)
  - Presentation (0.5mL)
  - Cold chain (stable at 2-8°C)

*EPI clinic near Lambarene, Gabon (Courtesy C. Cahill)*
RTS,S Pediatric Clinical Development Plan

**Decision 1: Go for pediatric development**
- Mal015: AS02A Ph I in 6-11yo Dose-escalation
- Mal020: AS02A Ph I in 1-5 yo Dose-escalation
- Mal025: AS02A Ph I in 1-4 yo Move to Mozambique

**Decision 2: Go for Phase II program**
- Pre-Mal 055: Pre study to prepare for Phase III
  - Mal055: AS01E Phase III, efficacy in children and infants

**Decision 3: Go for Phase III program**
- Mal050: AS01E, infants 6-12 wks, coad EPI
- Mal049: AS01E, 5-17m
- Mal047: 5-17m schedule optimization, AS02D-AS01E
- Mal046: AS01, 18m-4yr
- Mal040: AS02D, infants 6-12 wks, coad with EPI
- Mal038: AS02D, infants 6-10 wks, staggered with EPI
- Mal027: AS02A-AS01B Comparison Challenge trial, adults
- Mal034: AS02A-AS02D Bridging study, 3-5 yo
- Mal026: AS02A Ph II in 1-4 yo Proof of Concept
- Mal044: AS02A-AS01B Comparison, Kenyan adults
- Mal027: AS02A-AS01B Comparison Challenge trial, adults
- Mal028: AS02A Ph II in 1-4 yo Proof of Concept
- Mal029: AS02A Ph II in 1-4 yo Proof of Concept
- Mal030: AS02A Ph II in 1-4 yo Proof of Concept
- Mal031: AS02A Ph II in 1-4 yo Proof of Concept
- Mal032: AS02A Ph II in 1-4 yo Proof of Concept
- Mal033: AS02A Ph II in 1-4 yo Proof of Concept
- Mal034: AS02A-AS02D Bridging study, 3-5 yo
- Mal035: AS02A-AS02D Bridging study, 3-5 yo
- Mal036: AS02A-AS02D Bridging study, 3-5 yo
- Mal037: AS02A-AS02D Bridging study, 3-5 yo
- Mal038: AS02D, infants 6-10 wks, staggered with EPI
- Mal039: AS02D, infants 6-10 wks, staggered with EPI
- Mal040: AS02D, infants 6-12 wks, coad with EPI
- Mal041: AS02D, infants 6-12 wks, coad with EPI
- Mal042: AS02D, infants 6-12 wks, coad with EPI
- Mal043: AS02D, infants 6-12 wks, coad with EPI
- Mal044: AS02A-AS01B Comparison, Kenyan adults
- Mal045: AS02A-AS01B Comparison, Kenyan adults
- Mal046: AS02A-AS01B Comparison, Kenyan adults
- Mal047: 5-17m schedule optimization, AS02D-AS01E
- Mal048: 5-17m schedule optimization, AS02D-AS01E
- Mal049: AS01E, 5-17m
- Mal050: AS01E, infants 6-12 wks, coad EPI
- Mal051: AS01E, infants 6-12 wks, coad EPI
- Mal052: AS01E, infants 6-12 wks, coad EPI
- Mal053: AS01E, infants 6-12 wks, coad EPI
- Mal054: AS01E, infants 6-12 wks, coad EPI
- Mal055: AS01E Phase III, efficacy in children and infants
Vaccine Efficacy Across Four Phase IIb Trials

- **Infection**
  - Mal026: p=0.010
  - P<0.0001

- **Clinical Malaria**
  - Mal026: p=0.007
  - Mal038: p=0.06
  - P<0.001

- **Multiple Episodes**
  - Mal040: P<0.001
  - Mal047: P=0.014

- **Severe Malaria**
  - Mal026: P=0.019

Vaccine Efficacy (95% CI)

- 1 - 4 yrs
- 6 - 10 wks
- 1 - 4 yrs
- 6-10 wks
- 5 – 17 mos
- 1 - 4 yrs
- 5 – 17 mos
- 1 - 4 yrs

- Mal026
- Mal038
- Mal040
- Mal047

- AS02
- AS01
RTS,S Phase III Program

- 7 countries
- 11 centers
- Mix of malaria transmission settings
- $n \approx 14,000$

Our Approach to Global Access

- **Purpose**
  Philanthropy funds projects for the purpose of ultimately having an impact in the developing world, and not simply to advance science.

- **Principles**
  To achieve the following:
  » The knowledge gained through discovery must broadly and promptly be disseminated to the scientific community, and
  » Global health solutions must be accessible (price, supply and available) to people most in need in the developing world.