Malaria and vaccination: an update

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Malaria Control

• Drugs for treatment and/or prophylaxis
  Artemisinin-based Combination Therapy (ACT)

• Vector control
  Insecticide-impregnated nets (ITN)
  Indoor residual spraying (IRS)
Malaria prevalence in Africa

2000

2015

Problems in Malaria Control

- Drugs for treatment and/or prophylaxis
  - Resistance

- Vector control by pyrethroid impregnated bednets
  - Resistance

- Vaccines
Malaria Vaccine

**Aim:**

- At least 75% efficacy prevention of clinical disease
- To reduce transmission to enable elimination
  Start product development with the goal of transmission reduction

Vaccine targets in Plasmodium life cycle

- **Sporozoite/Liver stage vaccine**
- **Asexual stage vaccine**
- **Transmission stage vaccine**
Sporozoite/Liver stage Vaccines

Subunit

Candidates: RTS,S /AS01

Immune Mechanism: Antibody/CD4 CSP antigen

Vaccine Efficacy: ~30–50% decrease in clinical infection
Sub-unit Malaria Vaccine

RTS,S/AS01

Circumsorozoite protein

- Region I
- Central repeat region
- Region II
- Signal peptide
- GPI anchor sequence

Immunodominant B-cell epitope(s)
- NANP repeats

T-cell epitopes
- Variant
- Conserved
- CD4+ CD8+ CD4+

- HBsAg

TH2R TH3R CS.T3

HBsAg
The timeline for development of RTS,S spans >30 years

1984
GSK/WRAIR initiate collaboration

1987
RTS,S first created by combining the malaria CS protein and hepatitis B surface antigen

1995
First clinical tests in humans begin in adults in US

1998
First trials in Africa begin in Gambia

1997
Key proof-of-concept study shows 6 out of 7 volunteers in challenge trial are fully protected

2001
GSK/MVI partnership initiated

2004
Key Proof-of-Concept study in children in Mozambique

2007
Phase II results in African children and infants published in The Lancet and NEJM

2009
Phase III study start

2011
Phase III study
First results in 5-17 month olds 12 months follow up published in NEJM

2012
Phase III study
Second set of results in 6-12 week olds 12 months follow up published in the NEJM

2013
Phase III study
Results over 18 months follow-up first presented at MIM PAN African Malaria Conference with publication in PLoS Medicine 2014

2014
File submitted to the European Medicine Agency (EMA)

2015
EMA Positive Scientific Opinion granted

2015
Phase III study
Final results including 3-4 years of follow-up and 4th dose of RTS,S administered 18 months after the third dose published in The Lancet
Clinical Malaria Vaccine Trial RTS,S


Efficacy Phase IIb/III sub-unit vaccine trial in 15 000 children in 7 African countries:

- **RTS/S**: *P. falciparum* CSP fused to HBsAg/AS01E

  Protection:

  30-50% in children 6wks-17 mnth

NEJM 2011 365:1863; NEJM 2012 367 2283; NEJM 2013 368:1111

Efficacy in Controlled Human Malaria infection Model \(\sim\) 50%
Controlled Human Malaria infection (CHMI)
**Ethical considerations of CHMI**

Clinical trial in healthy(!) volunteers

**Benefit**
Maximize information

**Risk**
Safety first

• Conducted under rules of **Good Clinical Practice (GCP)**
  ı) the Committee for Proprietary Medical Products (CPMP) of the European Union; ii) the International Committee on Harmonization (ICH); iii) the Dutch Medical Research Involving Human Subjects Act (WMO), under the general ruling of the Clinical Trial Directive of the EU (2001/20/EU). Rules are based on the "Declaration of Helsinki" (World Medical Association Declaration of Helsinki).

• Approved by the **Central Committee involving Research in Human Subjects (CCMO)**, The Hague (http://www.ccmo-online.nl).

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Plasmodium cell cycle
Controlled Human Malaria infection (CHMI)

Bites of 5 Pf NF54 infected mosquitoes

Liver-stage

blood-stage

Thick smear (4000 Pf/ml)

qPCR (20 Pf/ml)

Treatment at thick-smear positive

Data from 48 volunteers in 7 CHMI trials
Roestenberg et al., JID, 2012

Sauerwein R et al, Nat Rev Immunol 2011

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Sporozoite/Liver stage Vaccines

**Subunit**
- **Candidates:** RTS,S /AS01
- **Immune Mechanism:** Antibody/CD4 CSP antigen
- **Vaccine Efficacy:** ~30–50% decrease in clinical infection

**Prime-Boost**
- **Candidates:** Viral +ChAd63/MVA + DNA/Ad5
  - *P. berghei* sporozoites
- **Immune Mechanism:** CD8 T cells 1–4 Antigens
- **Vaccine Efficacy:** ~20% short-term sterile protection
PbVac : Pb(PfCS@UIS4) genetically modified

Genetically modified *P. berghei* expressing *P. falciparum* CS Protein

PbVac immunization in rabbits delivered by 75 mosquito bites is:
- safe
- induces functional antibodies

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**PbVac: Phase 1/2a Clinical Trial**

**Stage 1: Safety**
- Dose-escalation

**Stage 2: Efficacy**
- \(n=12\)

**Add on**
- 15-40% Protected → Imm 5
- + Re-challenge
- >40% Protected →
  - unprotected: Imm 5 + Re-challenge
  - protected: Re-challenge

- period 2017-2018
Limited success of subunit vaccines

Insufficient breadth of the induced immune response

+ Mostly single antigens

+ Large genetic and antigenic variation in target antigens

*Attenuated whole parasite*
Sporozoite/Liver stage Vaccines

<table>
<thead>
<tr>
<th>Candidates:</th>
<th>Immune Mechanism:</th>
<th>Vaccine Efficacy:</th>
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<tr>
<td>Whole Sporozoite</td>
<td>CD8, CD4, γδ, NK cells Antibody Multiple Antigens</td>
<td>• Radiation-attenuated • Gene-attenuated • Chemo-prophylactic</td>
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</table>

- RTS,S /AS01
- ChAd63/MVA DNA/Ad5
- Prime
- Boost
- Radiant
- Adenovirus
- Chemo-prophylactic
Genetically attenuated parasites

Protection in CHMI >90% in Controlled Human Malaria Infection

- Mosquito bite 1000 Pf-infected mosquitoes
- Needle IV 10^6 cryopreserved sporozoites
**Stage 1: Dose escalation**

<table>
<thead>
<tr>
<th>Dose</th>
<th>PfΔb9Δslarp i.v</th>
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<tbody>
<tr>
<td>n=3</td>
<td>1x 1.35x10^5</td>
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<tr>
<td>n=3</td>
<td>1x 4.5x10^5</td>
</tr>
<tr>
<td>n=13</td>
<td>1x 9.0x10^5</td>
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**Primary Objective**
- Safety and tolerability

**Completed**

**Stage 2: Protective efficacy**

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<th>Dose</th>
<th>PfΔb9Δslarp i.v</th>
<th>PfSPZ Vaccine i.v</th>
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<tr>
<td>n=13</td>
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**Primary objective**
- Safety and tolerability

**Secondary objectives**
- Protective efficacy
CPS-CQ protocol

Chemo-Prophylaxis & Sporozoites with Chloroquine

Chloroquine (CQ)

Early stage

Mid stage

Later stage
Potent and dose-dependent CPS-CQ induced protection

**Diagram:**

- **Infectious mosquito bites under chloroquine cover**
- **Challenge infection**

Study month:

1  2  3

5-8
Potent and dose-dependent CPS-CQ induced protection

Homologous Protection after 3 month

CPS-CQ Immunization is potent

- Total of 30-45 Pf-infected mosquitoes
- Total of 150k Cryopreserved PfSPZ-CVac iv

Roestenberg & McCall et al NEJM, 2009
Bijker & Bastiaens et al PNAS, 2013
Bijker & Teirlinck et al JID 2014
Schars et al PloSOne 2015
Mordmueller et al Nature 2017
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Conclusion & next steps

• **Whole sporozoite immunization** is the most efficient method to induce high levels of sustained homologous protection in CHMI.

Next steps:

• Protection against other *P.falciparum* clones
• Potency of cryopreserved sporozoites
• Route of administration
• Define protective immune mechanism and responses:
Waiting for the Malaria Vaccine for > 25 years
Waiting for the Malaria Vaccine

Money
Tools
Expertise
Politics

Attenuated sporozoited
Vaccine targets in Plasmodium life cycle

Circumspz protein: CSP
Whole Sporozoites

Pfs48/45, Pfs230

RH5
Controlled Human Malaria infection (CHMI)

Sauerwein R et al, NRI 2011