Progress in the Hunt for a Malaria Vaccine

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Why do we need a malaria vaccine?

- In 2018, 405,000 deaths
- In 2018, 228 million cases
- In 2017, for the first time in a decade, the WHO reported an increase in the global incidence of malaria.
- Disruptions to healthcare and control programs caused by COVID could result in a doubling of malaria-related deaths.

Existing control methods (insecticides and anti-malarial drugs) increasingly less effective.

Why don't we have a malaria vaccine?

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Which Plasmodium species should a vaccine target?

-There are 6 species of malaria that infect humans.

What Plasmodium stage should be targeted?

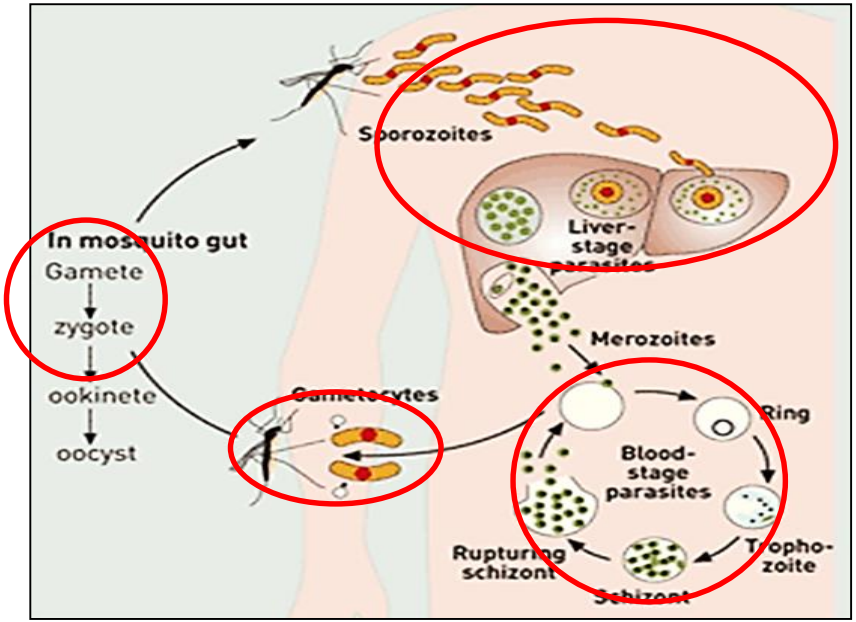
What do we want a malaria vaccine to do?

Requirements: affordable, capable of inducing long-term immunity, well tolerated and non-toxic

-eliminate infection?

-reduce disease?

-prevent transmission?



2 Broad Malaria Vaccine Approaches

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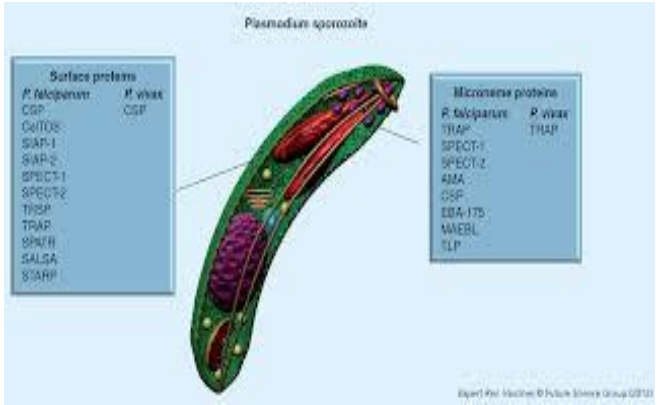
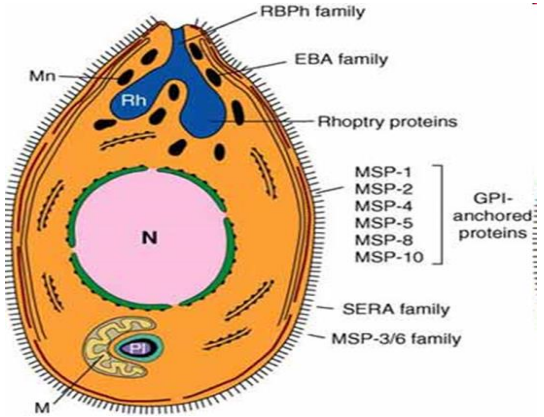
Sub-unit vaccines

- Contain a small part of the parasite eg a single protein
- Require adjuvants (substance that enhances immune response)
- Proteins that are targeted are often variable between different parasite strains
- Immune responses often not long-lived
- Low and variable protection





Whole Parasite Vaccines

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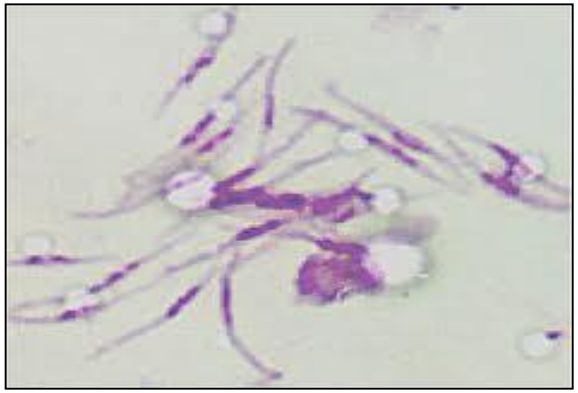
-Many different protein targets including proteins conserved between parasite strains

-May overcome issues associated with protein variation.



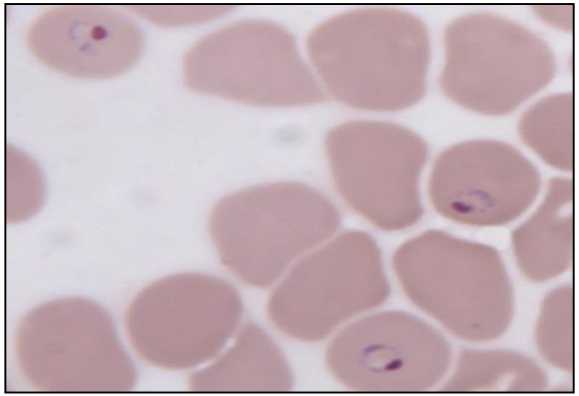
Approaches:

•Pre-erythrocytic:

-Irradiated sporozoite vaccine

-Chemically attenuated sporozoite vaccine

-Genetically attenuated sporozoite vaccine

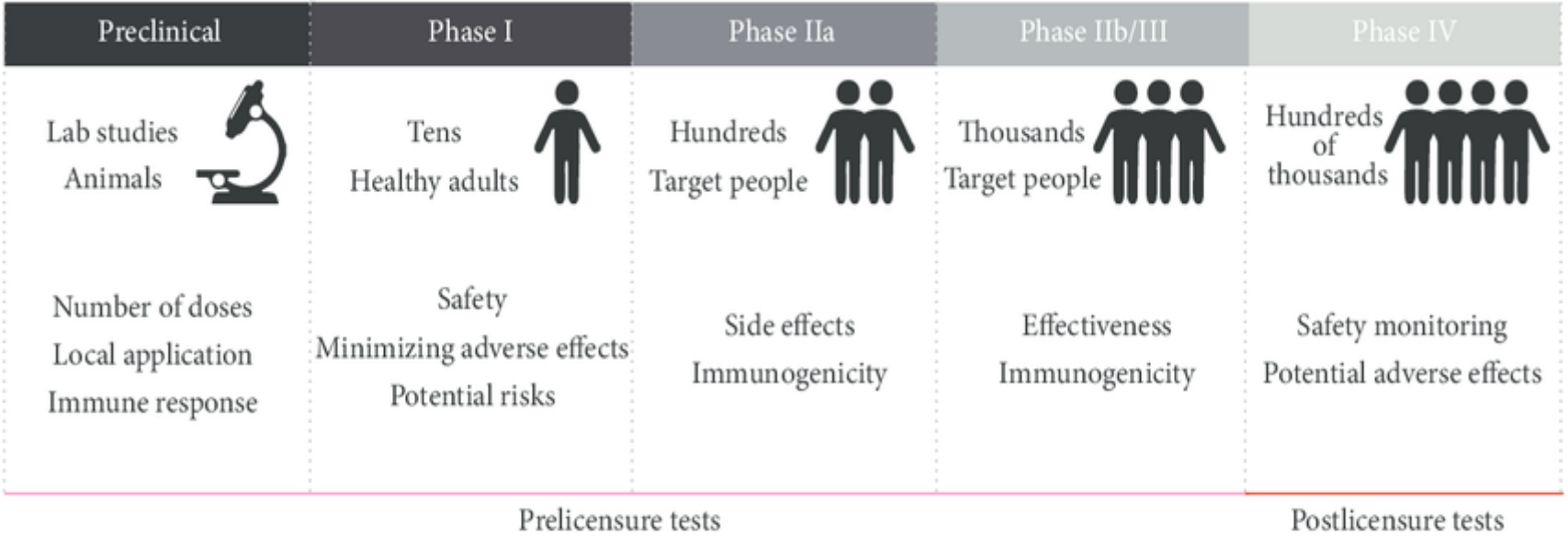


•Erythrocytic:

-Genetically attenuated blood-stage vaccine

-Chemically attenuated blood-stage vaccine

Evaluation and testing of vaccines



Immune response

Use challenge model

Placebo controlled

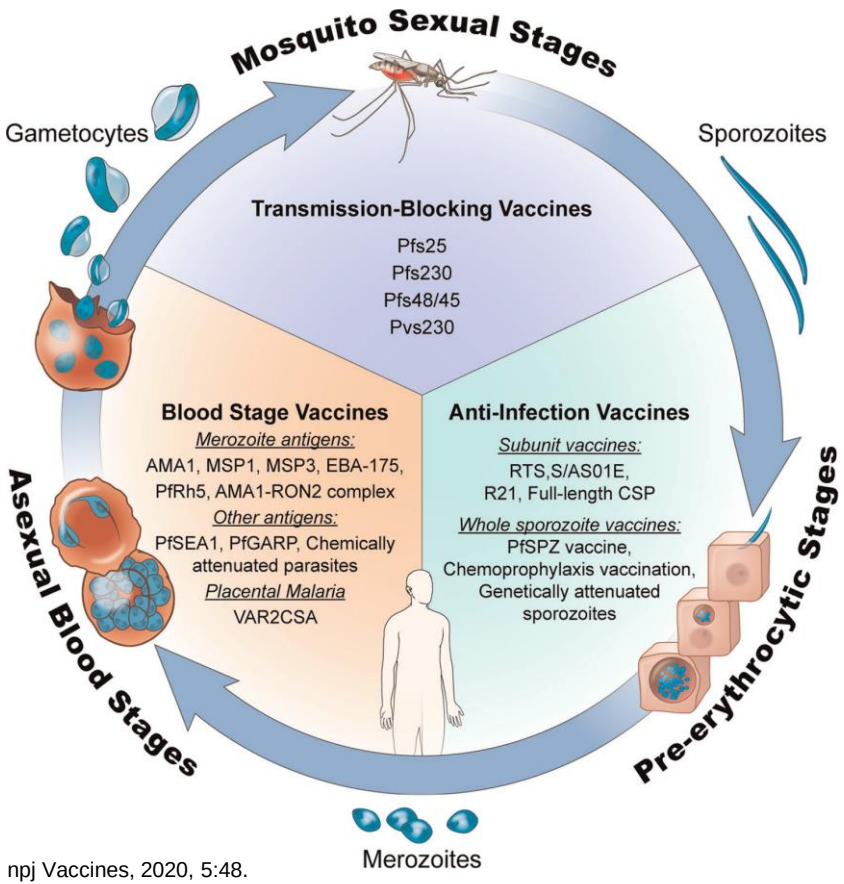
Double-blind

Rarer side effects

Average time: 12-15years

Cost: $US200-500 million per attempt.

Leading malaria vaccine candidates



Duffy et al, npj Vaccines, 2020, 5:48.

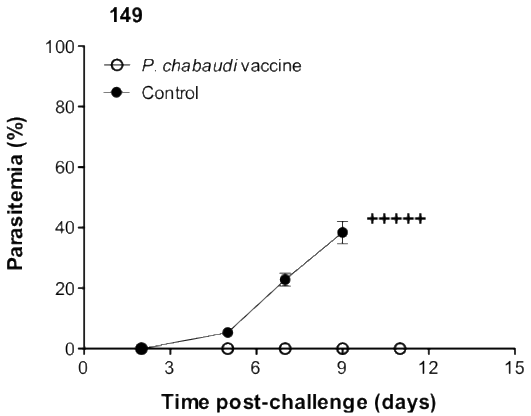
Table 2. Selected malaria vaccine candidates currently under preclinical development or in clinical trials.

Vaccine candidate	Immunogen type	Current status
Pre-erythrocytic stage (anti-infection)		
RTS,S	Subunit	Phase 4
R21	Subunit	Phase 1/2
Full-length CSP	Subunit	Phase 1
PfSPZ Vaccine	Whole sporozoite (radiation attenuation)	Phase 2
Chemoprophylaxis vaccination (CVac)	Whole sporozoite (chemical attenuation)	Phase 2
Genetically attenuated parasite (GAP) vaccines	Whole sporozoite (genetic attenuation)	Phase 1
Blood stage		
PfRH5	Subunit	Phase 1
AMA1-RON2	Subunit	Preclinical
PfSEA-1	Subunit	Preclinical
PfGARP	Subunit	Preclinical
Chemically attenuated parasite (CAP) vaccines	Whole blood-stage parasite	Phase 1
VAR2CSA (Placental malaria)	Subunit	Phase 1
PvDBP (*Plasmodium vivax*)	Subunit	Phase 1
Mosquito stage (Transmission-blocking)		
Pfs25	Subunit	Phase 1
Pfs230	Subunit	Phase 2
Pfs48/45	Subunit	Preclinical
Pvs230 (*Plasmodium vivax*)	Subunit	Preclinical

This table was adapted from a previous publication that has been updated to include more recent vaccine candidates[106]. Pre-erythrocytic, blood-stage and transmission-blocking vaccines are being evaluated in clinical trials (denoted as phases I to IV) or are being tested in rodent or non-human primate models (preclinical status).

Development of a chemically attenuated whole parasite blood-stage vaccine (PlasProtect)

- Tafuramycin-A binds to malaria parasite DNA and stops it replicating.
- In rodent models, chemically treated parasites (1 x 10^6 pRBC) can protect mice from challenge.
- Protection is dependent on CD4+ T cells.
- Red blood cell membranes must be intact for vaccine efficacy.



MF Good et al 2013 J Clin Invest 123(8): 3353-3362

A Raja et al 2016 Infect Immun 84(8): 2274-88

Reiman et al 2018 Clin Trans Immunol 7(4):e1015

Development and Evaluation of a Chemically Attenuated Malaria Vaccine

1. Pre-clinical Development: Establish protective efficacy and immune mechanisms in a rodent model of malaria.

2. **Pre-clinical Development: Develop key reagents for the chemically attenuated vaccine in humans.**

3. Clinical Development: Examine safety, tolerability and immunogenicity of vaccine in malaria naïve humans.

4. Clinical Development: Examine protective efficacy of vaccine in humans.

Clinical Vaccine Development

Development of *Plasmodium falciparum* cell banks

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Required:

- To make the vaccine
- For challenge to examine if the vaccine protects

P. falciparum parasites expanded in transfusion-grade Blood Group O Rh negative red blood cells in the cleanroom at Griffith University and then frozen.

Characterized according to specific release criteria eg sterility, viability of parasites, drug sensitivity profile, viral testing.

Suitable for administration to humans in early phase clinical studies.

DI Stanisic et al 2015 Malaria J 14: 143.

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Clinical study: Malaria Vaccine

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Pilot Study

1. **Identify correct dose of chemical to completely attenuate parasite**
2. **Examine safety and tolerability**
3. **Does it induce an immune response?**

Study participants screened according to inclusion/exclusion criteria

-Healthy males 18-60 years of age

-No history of clinical malaria or travel/residence (>2 weeks) in malaria endemic area within last 12 months

Vaccine Preparation

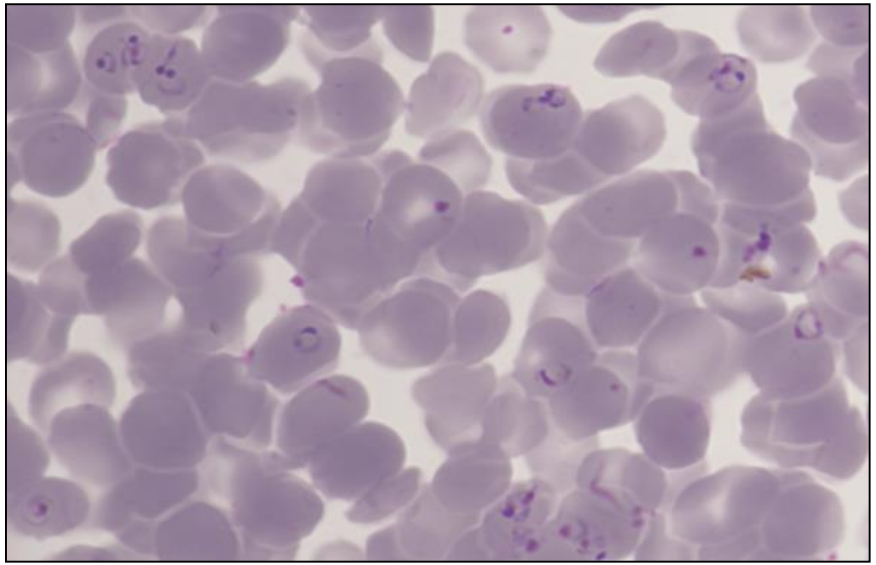
1. *P. falciparum* cell bank parasites thawed and cultured in Blood Group O Rh D negative red blood cells in cleanroom at Griffith University.

2. Parasites harvested.

3. Parasites treated with Tafuramycin-A.

4. Parasites washed.

5. Chemically treated parasites injected intravenously.



Clinical study: Malaria Vaccine

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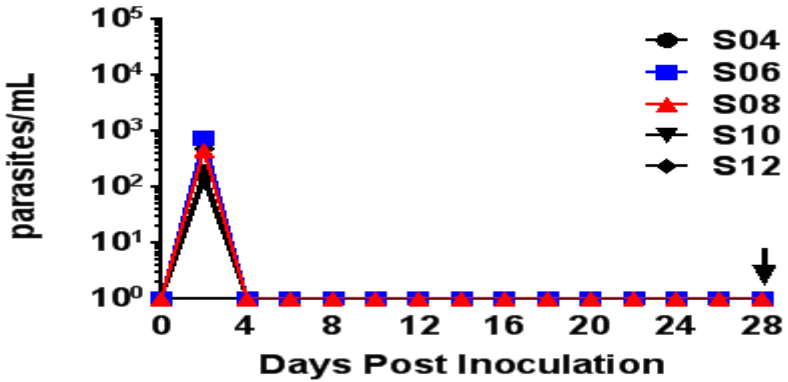
Study Group B:
Injected with one dose of chemically attenuated parasitised red blood cells



Broad T cell responses are induced by chemically attenuated blood-stage malaria parasites

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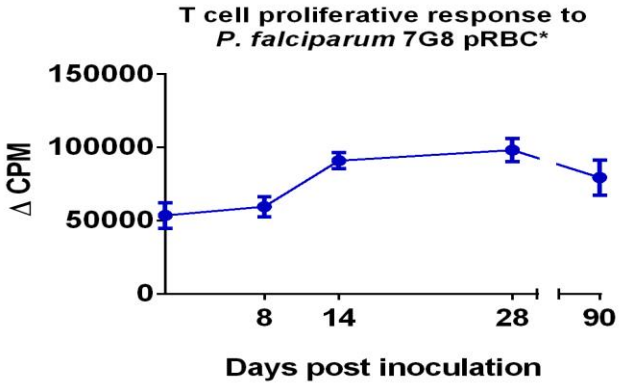

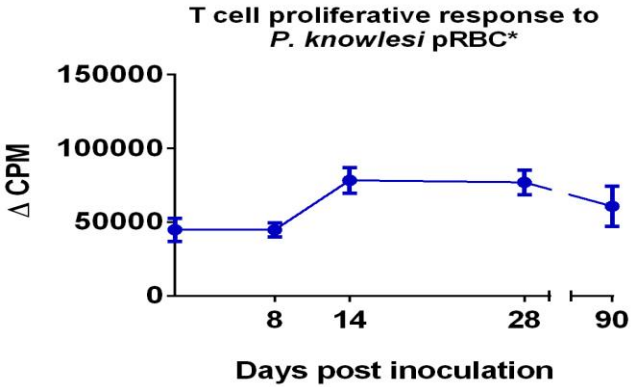

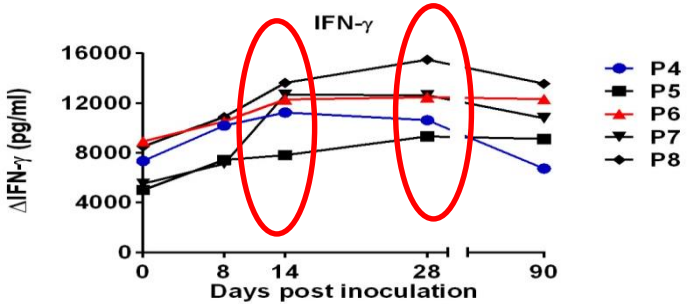

Cytokine producing memory T cells increase following inoculation with chemically attenuated blood-stage malaria parasites

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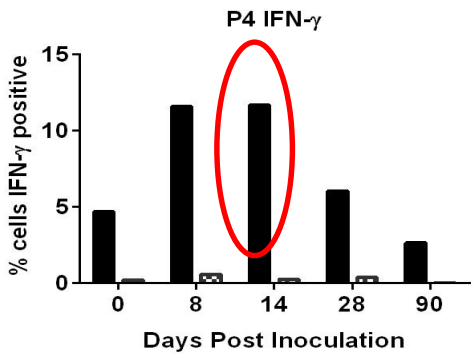

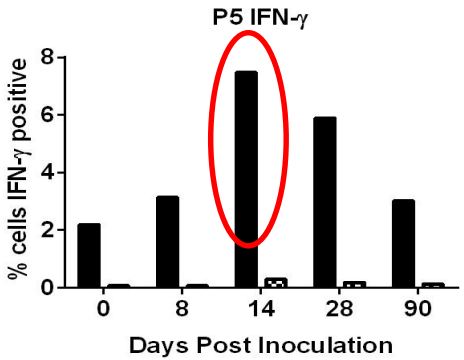

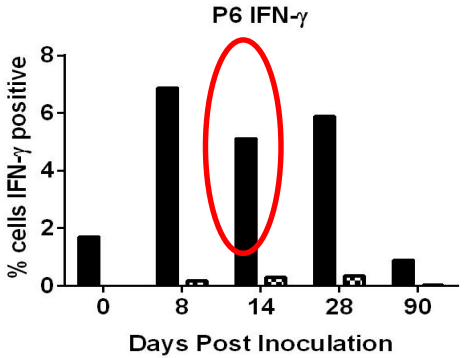

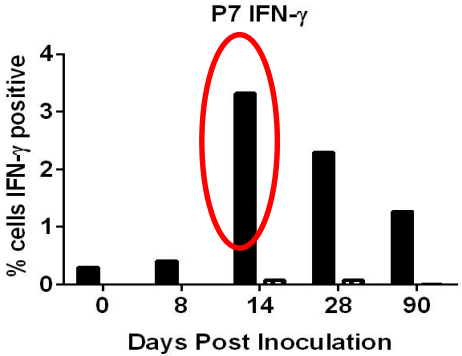

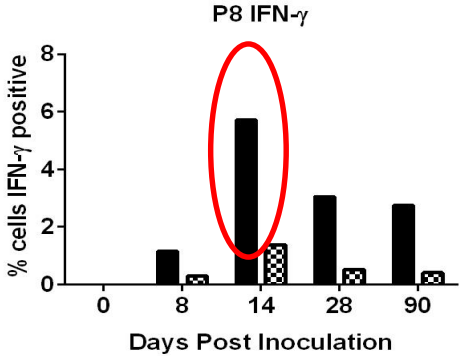

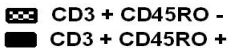

Chemically attenuated purified *P. falciparum* blood-stage vaccine

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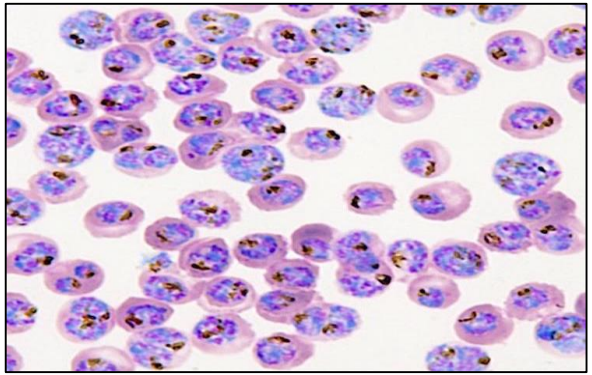
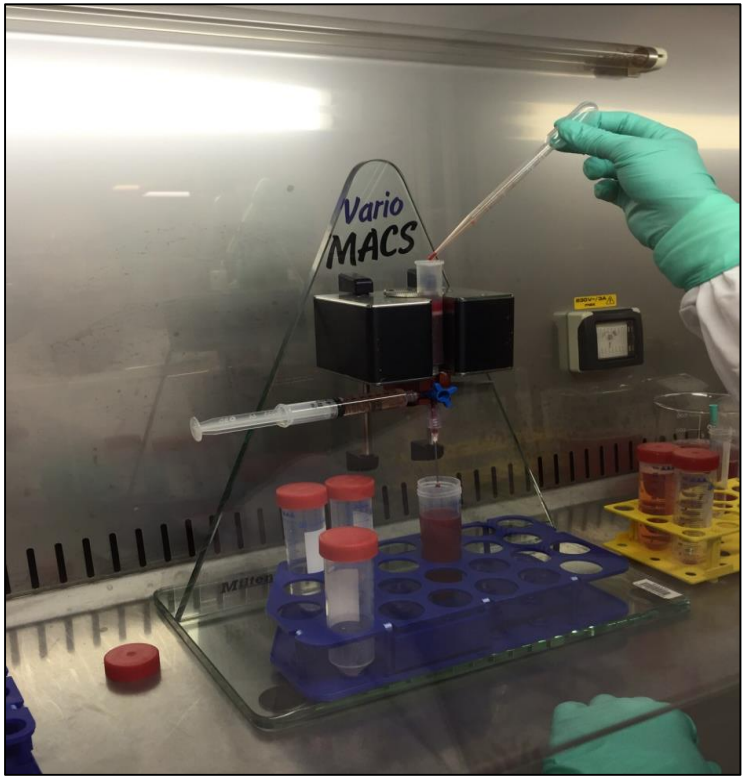
Vaccine has been reformulated

-contains purified parasitised red blood cells

-We have shown in a small pilot study that the fresh, purified form of the vaccine is safe and immunogenic.





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Phase Ib Efficacy Study (commenced)

Aims

Safety, immunogenicity and protective efficacy following blood-stage challenge

-2 study groups receiving different doses of parasite run sequentially

-1 or 2 infectivity controls per study group

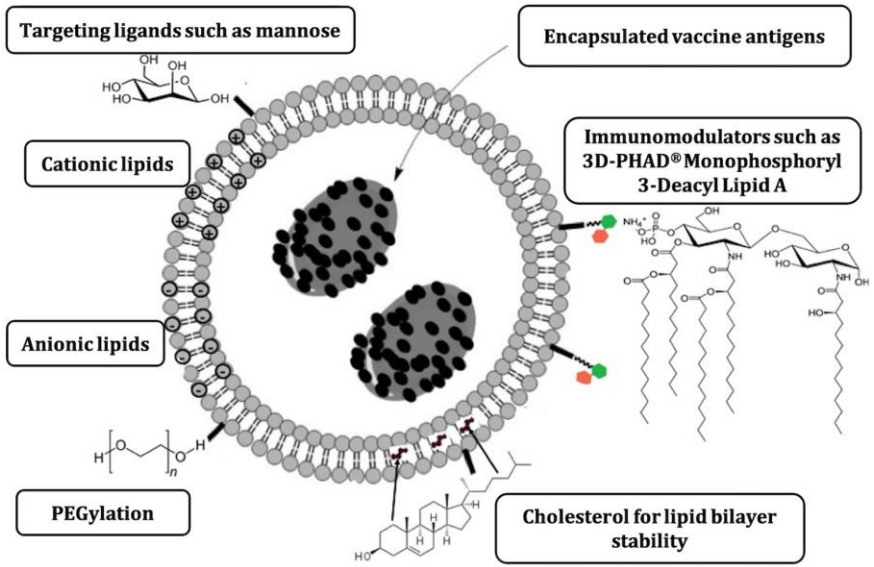
-3 doses of the vaccine on Day 0, 28 and 56

-Challenge one month later with infectious *P. falciparum* blood-stage parasites

-A proportion of vaccinees were fully protected against the challenge infection

Field deployable malaria vaccine

- Field-deployable vaccine = malaria parasites + liposomes
- Protective in rodent models of malaria
- Optimising vaccine candidate
- Produce vaccine candidate for toxicology tests and for clinical studies



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