The role of human infection challenge models to advance *P. vivax* vaccine development

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Can we accelerate vaccine development for *P. vivax*?
(and avoid mis-steps made in *P. falciparum* vaccine development?)

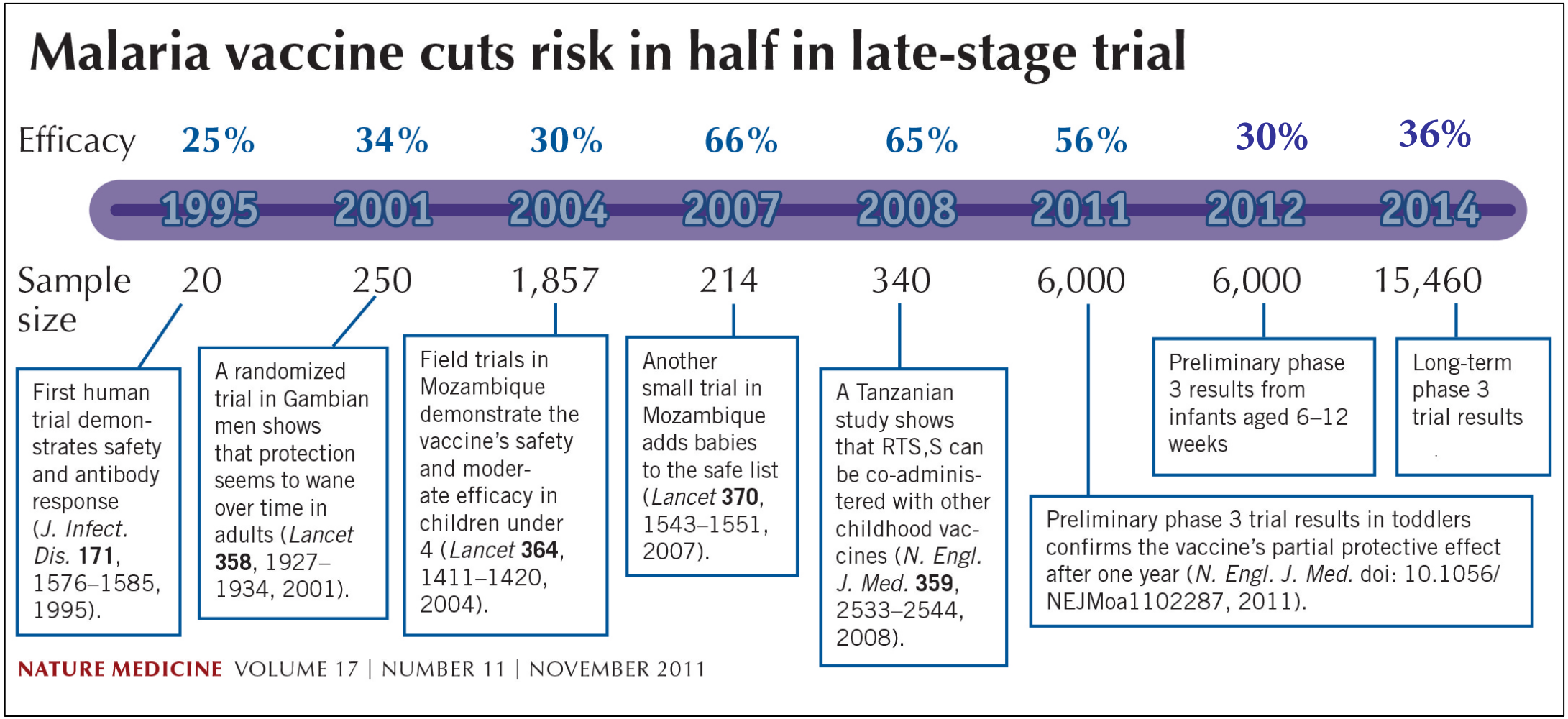
- Go faster?
- Not waste time or $!
- Exploit the potential of mRNA technology to accelerate vaccine development

Hybridoma Produces Protective Antibodies Directed Against the Sporozoite Stage of Malaria Parasite

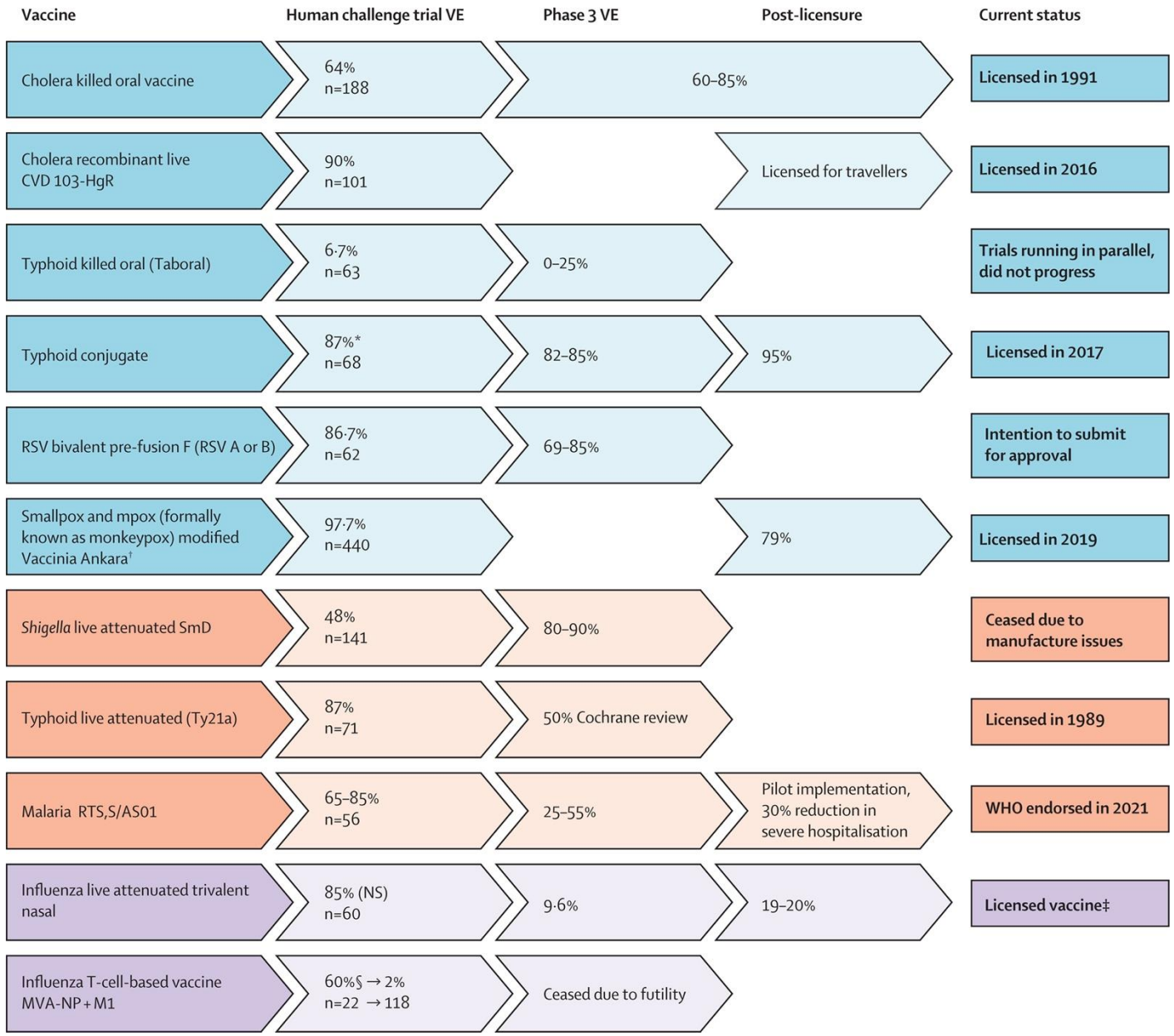
Abstract. *Hybrid cells secreting antibodies against sporozoites of* Plasmodium berghei *were obtained by fusion of plasmacytoma cells with immune murine spleen cells. The monoclonal antibodies bound to a protein with an apparent molecular weight of 44,000 (Pb44), which envelopes the surface membrane of sporozoites. Incubation of sporozoites in vitro with antibodies to Pb44 abolished their infectivity.*

Yoshida et al. Science. 1980;207:71-3.

The clinical development of RTS,S

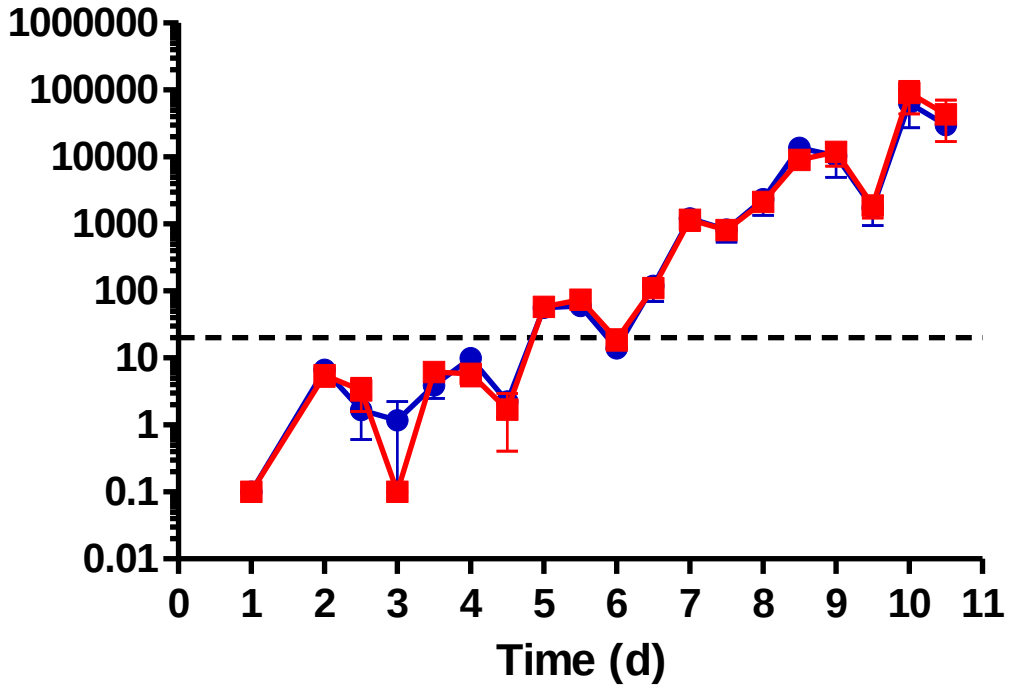


Using challenge studies to down-select vaccines



Abo et al, Lancet ID 2023

Challenge study shows lack of protection against blood-stage *P. falciparum* infection following vaccination with AMA1/ASO1



- Right vaccine antigen?
- Right immune response?
- Rate of growth of parasitemia

n=15 AMA1/ASO1B

n=15 control

Payne *et al* JID 2016

CHMI in malaria vaccine development

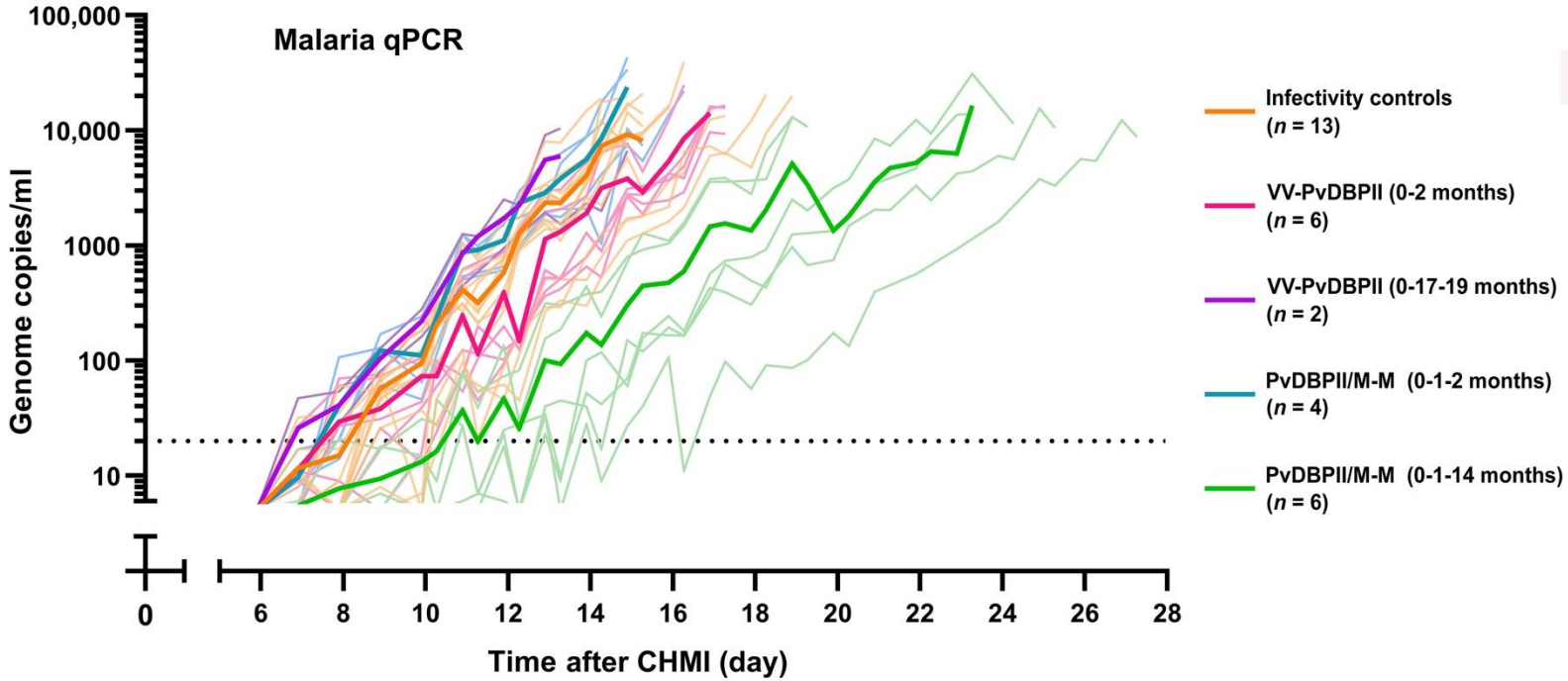
- Early efficacy assessments in malaria-naïve adults
  - Discard if no effect!
- Regimen optimization
  - Formulation (adjuvant), mRNA?
  - Dose, dose regimen
- Vaccine immunology
  - Intensive longitudinal sampling, systems immunology, correlates of protection
- Development of mAbs

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

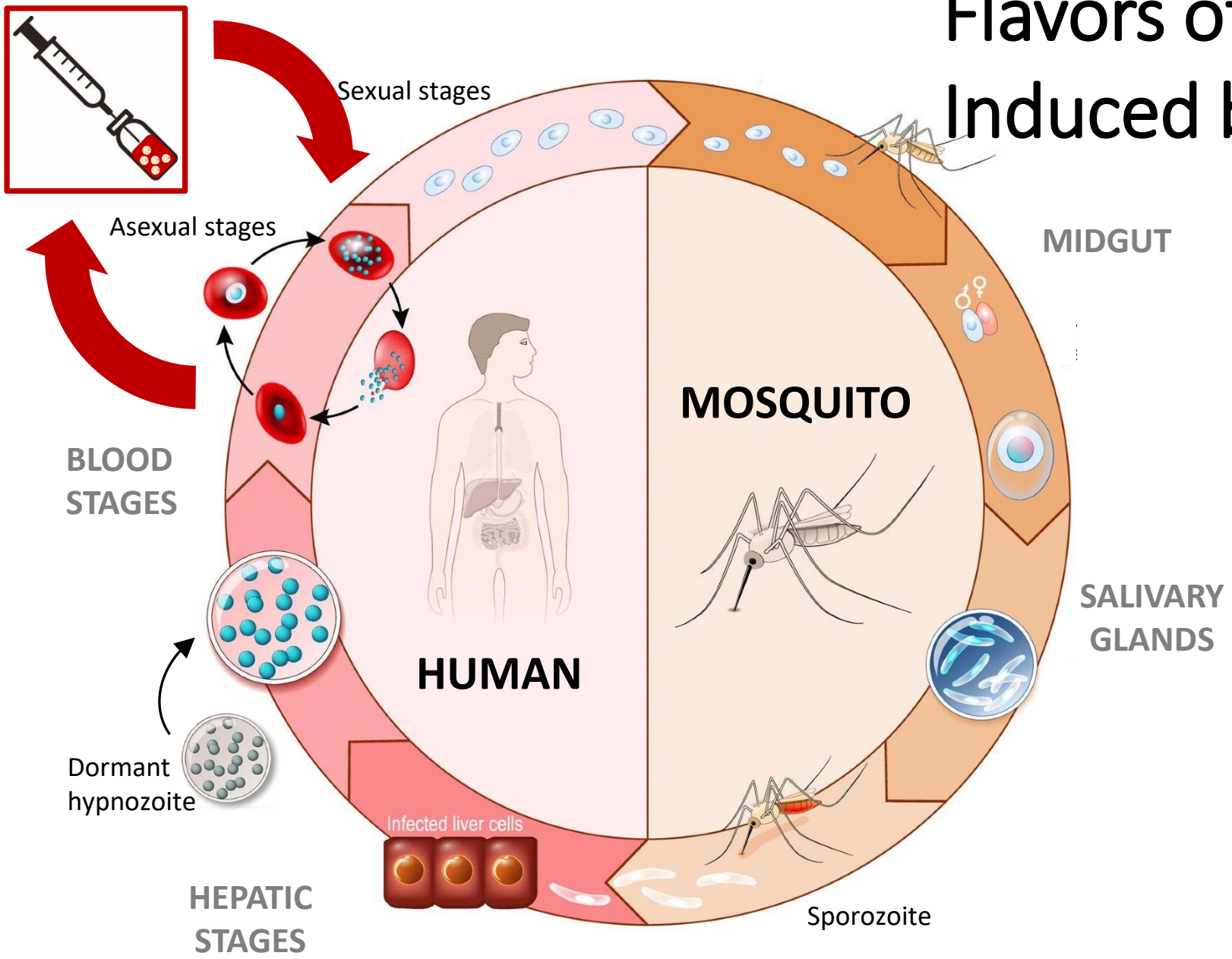
Vaccination with *Plasmodium vivax* Duffy-binding protein inhibits parasite growth during controlled human malaria infection

Mimi M. Hou[1,2,3], Jordan R. Barrett[1,2,3], Yrene Themistocleous[2], Thomas A. Rawlinson[2], Ababacar Diouf[4], Francisco J. Martinez[5], Carolyn M. Nielsen[1,2,3], Amelia M. Lias[1,2,3], Lloyd D. W. King[1,2,3], Nick J. Edwards[2], Nicola M. Greenwood[2], Lucy Kingham[2], Ian D. Poulton[2], Baktash Khozoee[2], Cyndi Goh[2], Susanne H. Hodgson[1,2,3], Dylan J. Mac Lochlainn[1,2,3], Jo Salkeld[1,2,3], Micheline Guillotte-Blisnick[5], Christèle Huon[5], Franziska Mohring[6], Jenny M. Reimer[7], Virander S. Chauhan[8], Paushali Mukherjee[9], Sumi Biswas[2], Iona J. Taylor[2], Alison M. Lawrie[2], Jee-Sun Cho[1,2,3], Fay L. Nugent[2], Carole A. Long[4], Robert W. Moon[6], Kazutoyo Miura[4], Sarah E. Silk[1,2,3], Chetan E. Chitnis[5]*, Angela M. Minassian[1,2,3,10]*†, Simon J. Draper[1,2,3,10]*†

There are no licensed vaccines against *Plasmodium vivax*. We conducted two phase 1/2a clinical trials to assess two vaccines targeting *P. vivax* Duffy-binding protein region II (PvDBPII). Recombinant viral vaccines using chimpanzee adenovirus 63 (ChAd63) and modified vaccinia virus Ankara (MVA) vectors as well as a protein and adjuvant formulation (PvDBPII/Matrix-M) were tested in both a standard and a delayed dosing regimen. Volunteers underwent controlled human malaria infection (CHMI) after their last vaccination, alongside unvaccinated controls. Efficacy was assessed by comparisons of parasite multiplication rates in the blood. PvDBPII/Matrix-M, given in a delayed dosing regimen, elicited the highest antibody responses and reduced the mean parasite multiplication rate after CHMI by 51% ($n = 6$) compared with unvaccinated controls ($n = 13$), whereas no other vaccine or regimen affected parasite growth. Both viral-vectored and protein vaccines were well tolerated and elicited expected, short-lived adverse events. Together, these results support further clinical evaluation of the PvDBPII/Matrix-M *P. vivax* vaccine.

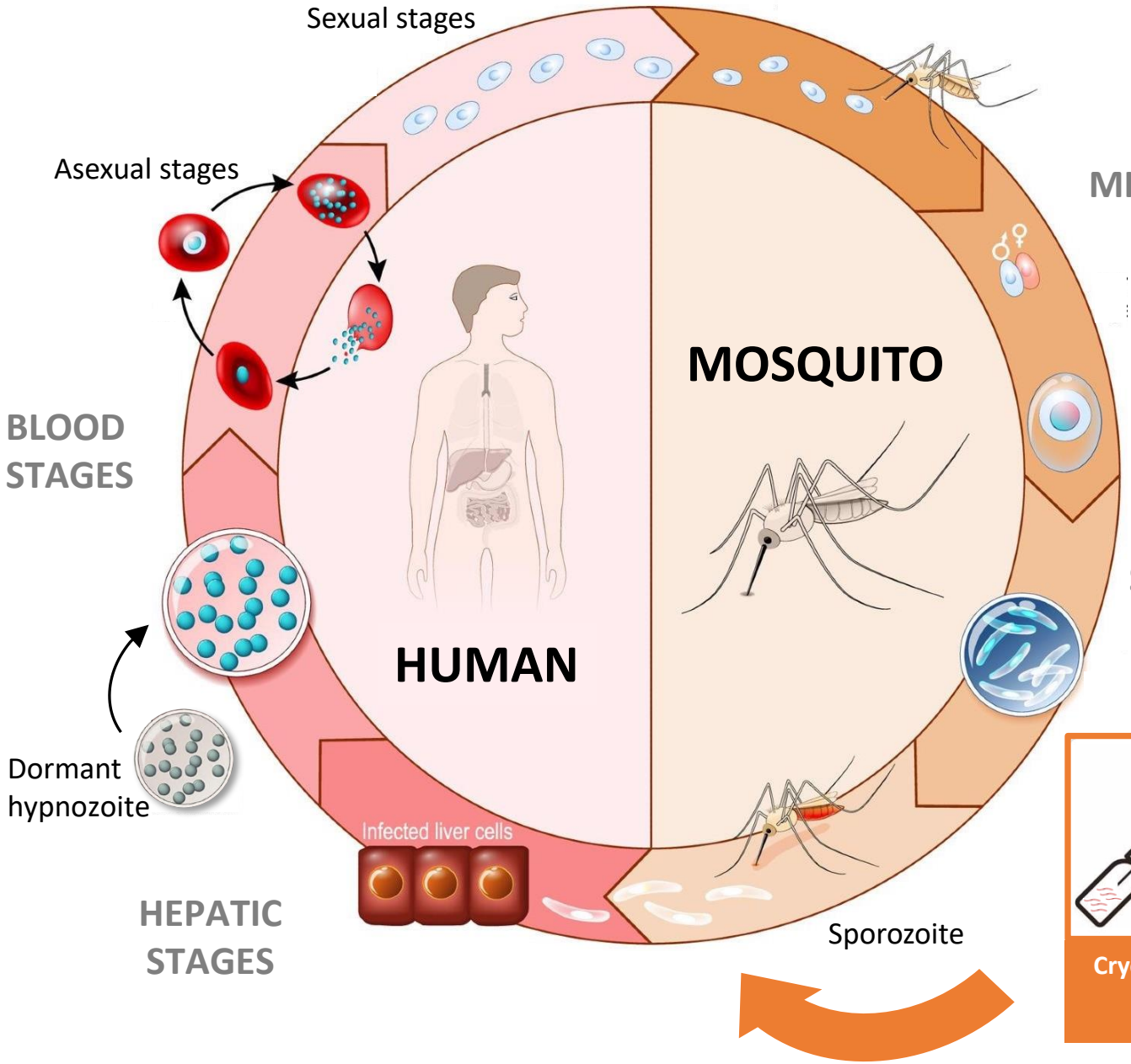

Malaria qPCR
Genome copies/ml
100,000
10,000
1000
100
10
0
6
8
10
12
14
16
18
20
22
24
26
28
Time after CHMI (day)
Infectivity controls
(n = 13)
VV-PvDBPII (0-2 months)
(n = 6)
VV-PvDBPII (0-17-19 months)
(n = 2)
PvDBPII/M-M (0-1-2 months)
(n = 4)
PvDBPII/M-M (0-1-14 months)
(n = 6)

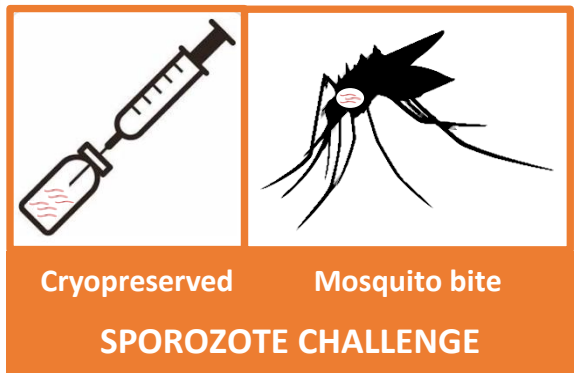
Flavors of *P. vivax* CHMI: Induced blood stage malaria



- Reproducible
- Fast
- Assess blood stages
- Does not evaluate liver stages

Flavors of *P. vivax* CHMI: Sporozoite challenge





- Assess all stages
- Relapse risk
- Harder to reproduce

Need for new tools to control *P. vivax*

- **Challenges with detection**
  - RDTs relatively insensitive
  - Silent hypnozoite reservoir
- **Radical cure is difficult**
  - Individual, population levels
  - PK/PD/pharmacogenomics
- **ITN may be less effective**
- **Monitoring progress is difficult**
  - EIR has less impact on prevalence

How can we fully assess an AIV?

Would a TBV or BSV contribute more?

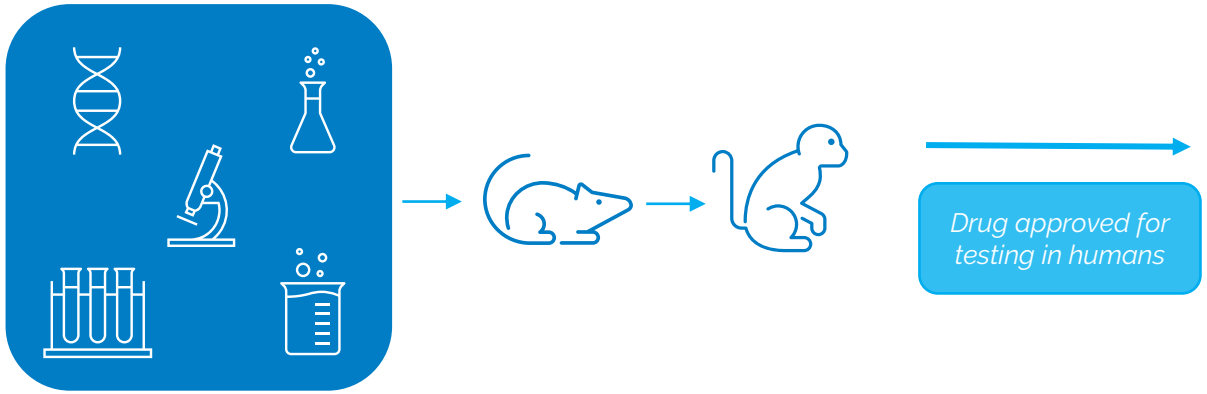
What kind of durability is needed?

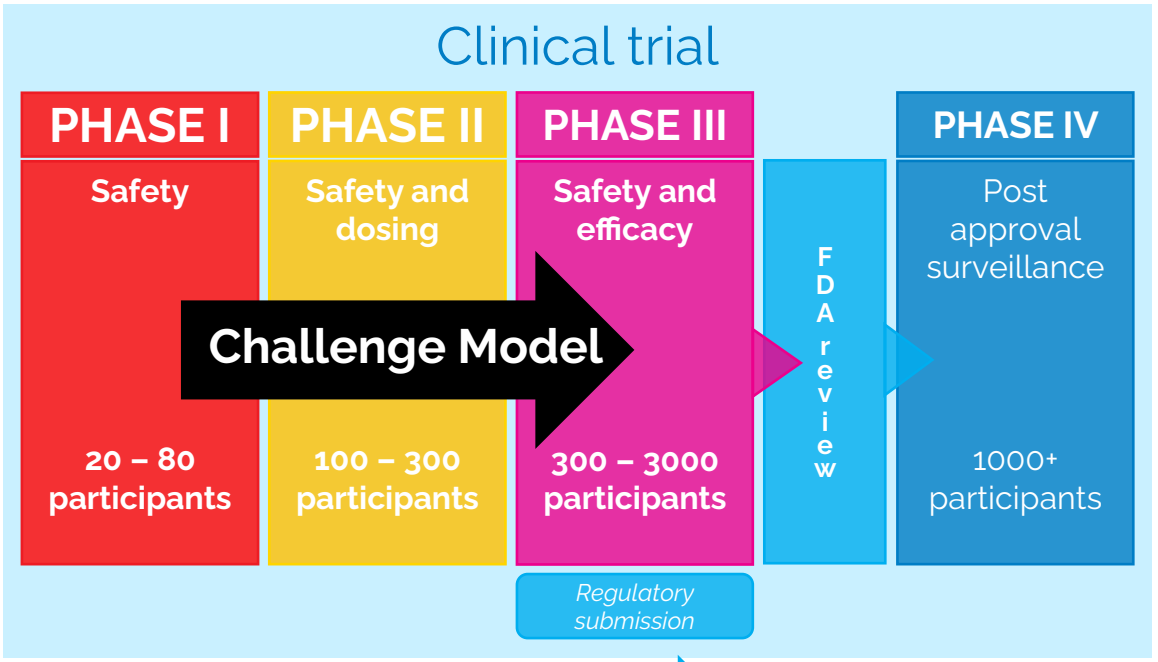
CHMI in *P. vivax* vaccine development

- **CHMI platforms can be configured to suit stage specific interventions**
  - Capacity in non-endemic and endemic regions
  - Increasing standardization of approach and scalability
- **Accelerate vaccine development**
  - Down select
  - Compare targets
  - Compare formulations, doses and regimens (?mRNA)
  - Rapid transfer from phase 1 to testing new candidates
  - ? Accelerated regulatory approval
- **Enrich vaccine development pipeline**
  - Host and parasite response studies
  - Surrogates of protection
  - Systems immunology

Problem statement: how can we shorten the vaccine development journey?

Post COVID-19





<9 months

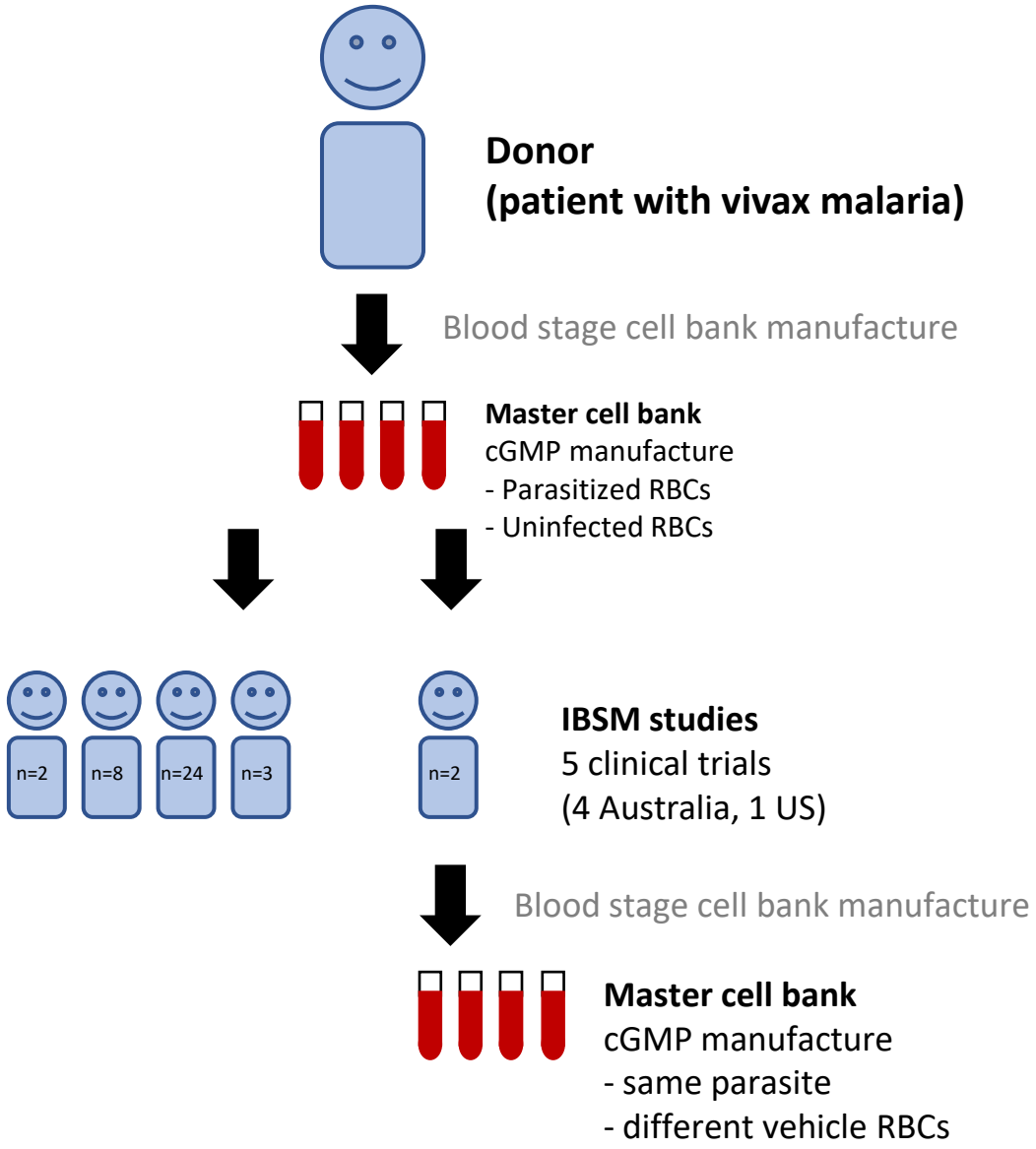
These trials accelerate understanding of host pathogen interactions in humans by enabling prospective studies of infection from baseline, through active pathogen replication to cure/immunity.

CHIM (Controlled Human Infection Models) in mRNA vaccine development

- **Can CHIM models be implemented to accelerate POC studies of mRNA vaccines?**
  - POC
  - Down select
  - Compare targets
  - Compare formulations, doses and regimens
  - Rapid transfer from phase 1 to testing new candidates
  - ? Accelerated regulatory approval
- **Enrich vaccine development pipeline**
  - Host and parasite response studies
  - Surrogates of protection
  - Systems immunology

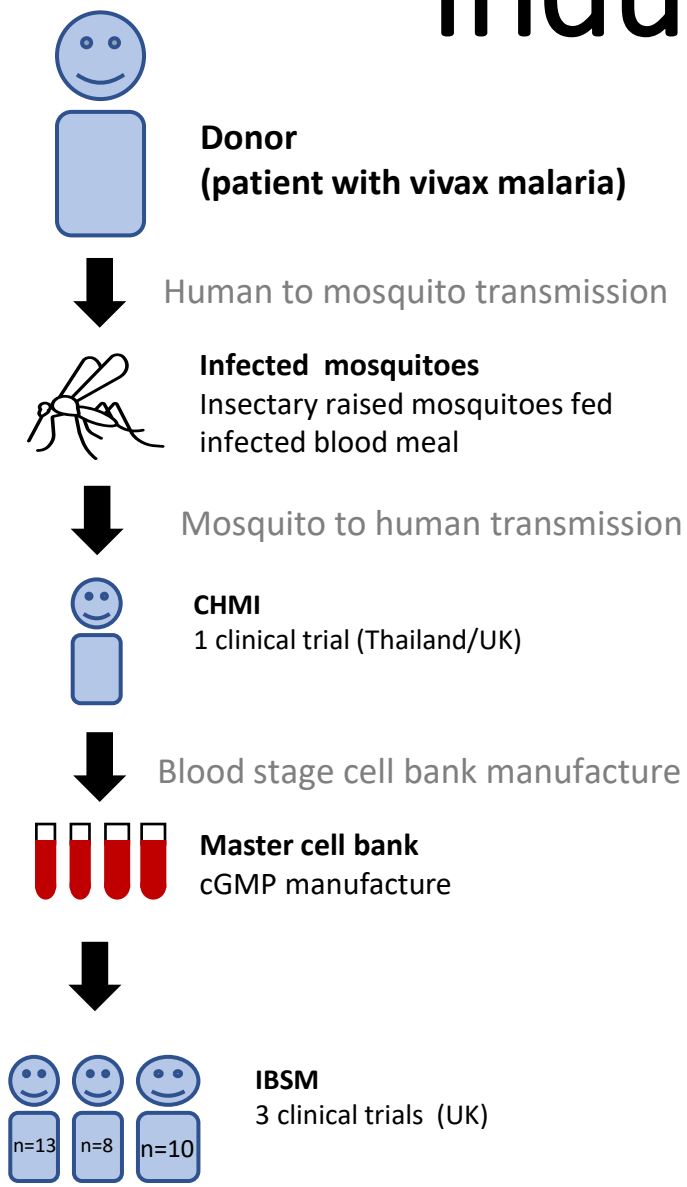
Thank you!

Induced blood stage malaria - i



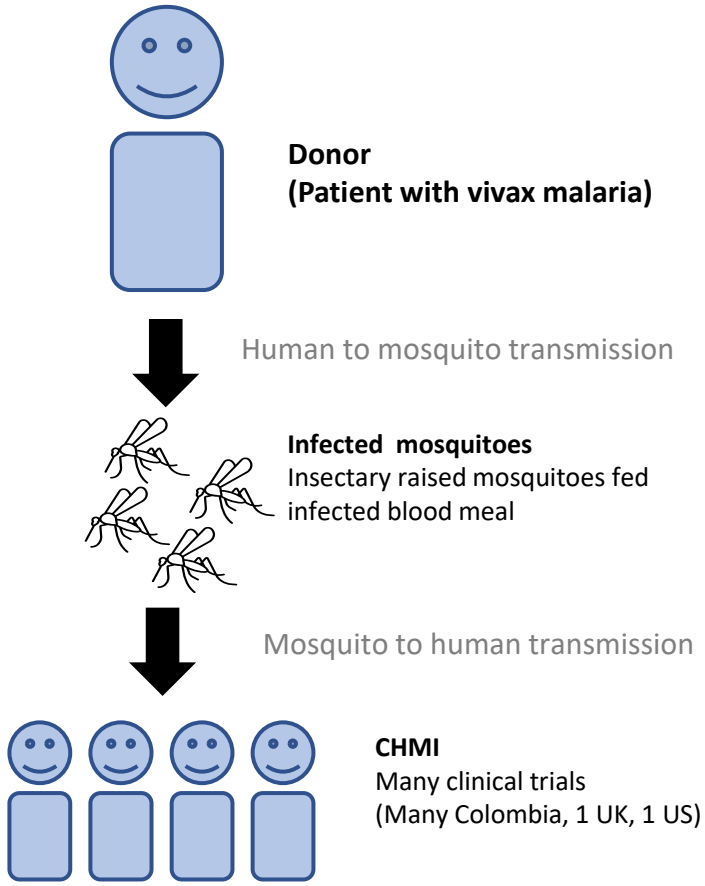
- Challenge agent:
  - Parasitized red blood cells prepared from master cell banks
- Readily scalable and transferable
- Suited to studies in endemic and non-endemic regions

Induced blood stage malaria - ii



- Parasitized red blood cell challenge agent prepared from master cell banks
- Readily scalable and transferable
- Suited to studies in endemic and non-endemic regions

Sporozoite challenge - i

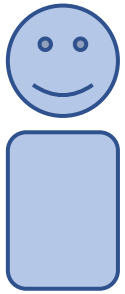


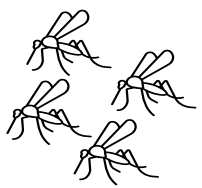
- Mosquito bite challenge prepared using lab colonies
- Parasite always different
- Logistically difficult
- Harder to scale and transfer
- Suited for studies in endemic regions

Sporozoite challenge - ii

Experimentally infected Saimiri monkey

Experimentally infected volunteer Donor

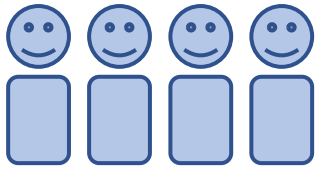




Infected mosquitoes
Insectary raised mosquitoes fed infected blood meal

SPZ harvested from mosquito salivary glands

Vialled SPZ challenge



CHMI

- SPZ challenge prepared using GMP SPZ
- Logistically easier for trials
- Not yet implemented

Challenges to *P. vivax vaccine* development arising from the parasite's biology and epidemiology

- **Relapsing infections**
  - Hypnozoite burden/reservoir
  - Periodicity of relapse
- **Lower blood-stage parasitemia**
  - Reticulocyte invasion
  - Less severe / acute illness
- **Greater transmissibility**
  - Early gametocyte maturation
  - More efficient transmission
  - Asymptomatic transmission
- **Lower prevalence, seasonality**
- **Wider geographic distribution**
  - Diverse population and climate
- **Vector ecology**
  - Large number
  - Diversity in behavior, location
- **Co-endemicity**
  - Relative proportion over time
  - Missed co-infection

P. vivax control

- ***P. vivax* elimination will be difficult**
  - After *P. falciparum* leaves, *P. vivax* remains
  - Relapsing infections affect bottlenecks targeted by vaccines
  - Lack of *in vitro* culture makes biologic studies difficult

- ***P. vivax* vaccine field testing will be difficult**
  - Lack of intense seasonal transmission regions seen for *P. falciparum*
  - Most cases are relapses, inability to differentiate
  - Less funding available for *P. vivax* R&D

Can *P. vivax* CHMI accelerate Pv vaccine development?