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

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Can we accelerate vaccine development for \textit{P. vivax}? (and avoid mis-steps made in \textit{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.
The clinical development of RTS,S

### Malaria vaccine cuts risk in half in late-stage trial

<table>
<thead>
<tr>
<th>Year</th>
<th>Efficacy</th>
<th>Sample Size</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>34%</td>
<td>250</td>
<td>A randomized trial in Gambian men shows that protection seems to wane over time in adults (Lancet 358, 1927-1934, 2001).</td>
</tr>
<tr>
<td>2004</td>
<td>30%</td>
<td>1,857</td>
<td>Field trials in Mozambique demonstrate the vaccine’s safety and moderate efficacy in children under 4 (Lancet 364, 1411-1420, 2004).</td>
</tr>
<tr>
<td>2007</td>
<td>66%</td>
<td>214</td>
<td>Another small trial in Mozambique adds babies to the safe list (Lancet 370, 1543-1551, 2007).</td>
</tr>
<tr>
<td>2008</td>
<td>65%</td>
<td>340</td>
<td>A Tanzanian study shows that RTS,S can be co-administered with other childhood vaccines (N. Engl. J. Med. 359, 2533-2544, 2008).</td>
</tr>
<tr>
<td>2011</td>
<td>56%</td>
<td>6,000</td>
<td>Preliminary phase 3 results from infants aged 6–12 weeks.</td>
</tr>
<tr>
<td>2012</td>
<td>30%</td>
<td>6,000</td>
<td>Long-term phase 3 trial results.</td>
</tr>
</tbody>
</table>
Using challenge studies to down-select vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Human challenge trial VE</th>
<th>Phase 3 VE</th>
<th>Post-licensure</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholera killed oral vaccine</td>
<td>64% n=188</td>
<td>60-85%</td>
<td></td>
<td>Licensed in 1991</td>
</tr>
<tr>
<td>Cholera recombinant live CVD 103-HgR</td>
<td>90% n=101</td>
<td></td>
<td>Licensed for travellers</td>
<td>Licensed in 2016</td>
</tr>
<tr>
<td>Typhoid killed oral (Tiboral)</td>
<td>6.7% n=63</td>
<td>0-25%</td>
<td></td>
<td>Trials running in parallel, did not progress</td>
</tr>
<tr>
<td>Typhoid conjugate</td>
<td>87%* n=68</td>
<td>82-85%</td>
<td>95%</td>
<td>Licensed in 2017</td>
</tr>
<tr>
<td>RSV bivalent pre-fusion F (RSV A or B)</td>
<td>86.7% n=82</td>
<td>69-85%</td>
<td></td>
<td>Intention to submit for approval</td>
</tr>
<tr>
<td>Smallpox and rinderpest (formally known as monkeypox) modified Vaccinia Ankara¹</td>
<td>97.7% n=440</td>
<td></td>
<td>79%</td>
<td>Licensed in 2019</td>
</tr>
<tr>
<td>Shigels live attenuated SMd</td>
<td>48% n=141</td>
<td>80-90%</td>
<td></td>
<td>Ceased due to manufacture issues</td>
</tr>
<tr>
<td>Typhoid live attenuated (Ty21a)</td>
<td>87% n=71</td>
<td></td>
<td>50% Cochrane review</td>
<td>Licensed in 1989</td>
</tr>
<tr>
<td>Malaria RTS,S/AS01</td>
<td>65-83% n=56</td>
<td>25-55%</td>
<td>Pilot implementation, 30% reduction in severe hospitalisation</td>
<td>WHO endorsed in 2021</td>
</tr>
<tr>
<td>Influenza live attenuated trivalent nasal</td>
<td>85% (NS) n=60</td>
<td>9.6%</td>
<td>19-20%</td>
<td>Licensed vaccine¹</td>
</tr>
<tr>
<td>Influenza T-cell-based vaccine MVA-NP+M1</td>
<td>60%5 → 2% n=22 → 118</td>
<td></td>
<td></td>
<td>Ceased due to futility</td>
</tr>
</tbody>
</table>

¹ Smallpox and rinderpest (formally known as monkeypox) modified Vaccinia Ankara

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

\[ \text{n=15 AMA1/ASO1B} \]
\[ \text{n=15 control} \]

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
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. Lis\(\text{a}\)\(^1,2,3\), Lloyd D. W. King\(^1,2,3\), Nick J. Edwards\(^2\), Nicola M. Greenwood\(^2\), Lucy Kingham\(^2\), Ian D. Poulton\(^2\), Baktash Khazoe\(\text{e}\)\(^2\), 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\(^9\), 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 chim-panzee 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.
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

Clinical trial

PHASE I
- Safety
- 20 – 80 participants
- Drug approved for testing in humans

PHASE II
- Safety and dosing
- 100 – 300 participants

PHASE III
- Safety and efficacy
- 300 – 3000 participants

PHASE IV
- Post approval surveillance
- 1000+ participants

<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

Donor (patient with vivax malaria)

Blood stage cell bank manufacture

Master cell bank
cGMP manufacture
- Parasitized RBCs
- Uninfected RBCs

IBSM studies
5 clinical trials
(4 Australia, 1 US)

Blood stage cell bank manufacture

Master cell bank
cGMP manufacture
- same parasite
- different vehicle RBCs
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

Donor (Patient with vivax malaria)

Human to mosquito transmission

Infected mosquitoes
Insectary raised mosquitoes fed infected blood meal

Mosquito to human transmission

CHMI
Many clinical trials
(Many Colombia, 1 UK, 1 US)
Sporozoite challenge - ii

- 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

- **Vector ecology**
  - Large number
  - Diversity in behavior, location
**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?