The role of CHIM studies in accelerating malaria vaccine development: lessons learned from Kenya

Melissa Kapulu
WHO/MPP mRNA Technology Transfer Programme Meeting
19th April 2023
KEMRI-Wellcome Trust Research Programme
“Human infection studies (also known as human challenge trials and controlled human infection models) have the power to rapidly accelerate the development of much-needed vaccines and treatments……”

Purified cryopreserved sporozoites – PfSPZ Challenge

Modified from Kibwana, Kapulu, Bejon 2022

TBM: Transmission-blocking model
IBSM: Induced blood-stage model

Vaccine efficacy
Infectivity

<100
TBM
IBSM

<50
Infectivity

>100
Vaccine efficacy
Infectivity

>100
Vaccine efficacy

>200
Infectivity
Vaccine efficacy
TBM
IBSM

Purified cryopreserved sporozoites – PfSPZ Challenge

SANARIA

CHMI in Africa

KEMRI Wellcome Trust

Modified from Kibwana, Kapulu, Bejon 2022
Role of CHMI in Malaria Vaccine Development

**Anti-Infection stage**
- One Major Antigen
- Proof of principle efficacy in CHMI
- Progress onto clinical trials in target population
  - 100s of children

**Anti-Disease stage**
- Select antigen(s) by study of immunity
- Proof of principle efficacy in CHMI
- Progress onto clinical trials in target population
  - 100s of children

**Anti-Transmission stage**
- Several lead antigens
- Proof of principle efficacy in CHMI
- Progress onto clinical trials in target population
  - 100,000s of people
Rationale for Malaria Challenge Studies in Semi-Immune Adults?

- [Better] Understand Naturally Acquired Immunity
  - Correlates (surrogate markers) of immunity/infection

- Accelerate Vaccine Development
  - Target antigen discovery and development

- Test Efficacy of Vaccines (and/or drugs/treatments)
  - Correlates (surrogate markers) of protection
## Controlled Human Malaria Infection Platform

<table>
<thead>
<tr>
<th>Study</th>
<th>Funder</th>
<th>No. of Volunteers</th>
<th>Aim</th>
<th>Status</th>
<th>Vaccine Antigen Discovery</th>
<th>Test Vaccines</th>
<th>Transmission Model</th>
<th>Blood-stage Model</th>
<th>Vivax (led by MORU, Thailand)</th>
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<td>Wellcome</td>
<td>161</td>
<td>Vaccine Efficacy</td>
<td>Completed (2021)</td>
<td>EDCTP</td>
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<td>EDCTP</td>
<td>80</td>
<td>Test Blocking of Mosquito Infectivity</td>
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<td>Test Sterile Immunity to Blood-Stages</td>
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<td>Vaccine Antigen Discovery</td>
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</table>

**Plasmodium falciparum**

**Plasmodium vivax**

Embedded Social science and empirical ethics research across all studies
Controlled Human Malaria Infection in Our Setting

Day 0: Inject Sporozoites

Days 7 onwards: parasites multiply in blood, opposed by immunity

Day 0-6: Liver Incubation

Use Daily qPCR to quantify parasites

Follow up for 21 days and endpoint treatment with Artemether Lumefantrine (3 day observed)

*Sickle cell trait an exclusion criteria
Healthy semi-immune adults with varying degrees of immunity (screened for range of natural exposure) from:

- Ahero – moderate-high exposure
- Kilifi South – moderate exposure
- Kilifi North – low to no exposure

Adapted from Kapulu et al 2019
Key Outcome following CHMI

- **Highly immune Phenotype**
- **Clearance Phenotype**
- **Slow Growth Phenotype**
- **Susceptible Phenotype**

Endpoint Treatment

Parasitaemia

Time (days)

3,200 Sporozoites

Infection

Sporozoites
Parasite growth following CHMI

Kapulu et al. 2021

- Parasites Detected and Treatment Needed
  - Febrile Episode

- Parasites Detected but no Treatment Needed
  - No Parasites Detected

Graphs showing parasite growth over time in different locations:
- a) Nairobi
- b) Kilifi North
- c) Kilifi South
- d) Ahero

Kapulu et al. 2021
## Multi-stage Vaccine Efficacy in CHMI

Recruitment from Kilifi North – low exposure population

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<th>Week</th>
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<th>4</th>
<th>8</th>
<th>12</th>
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<tr>
<td>R21 (ID) N=24</td>
<td>R21/ Matrix M 10µg /50µg</td>
<td>R21/ Matrix M 10µg /50µg</td>
<td>R21/ Matrix M 10µg /50µg</td>
<td>CHMI (ID)</td>
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<tr>
<td>ME-TRAP (ID) N=24</td>
<td>ChAd63 ME-TRAP 5x10^10 vp</td>
<td></td>
<td>MVA ME-TRAP 2x10^8 pfu</td>
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<td>R21/ Matrix M 10µg /50µg</td>
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<td>CHMI (DVI)</td>
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<td>Control (ID) N=18</td>
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<td>CHMI (ID)</td>
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ClinicalTrials.gov Identifier: NCT03947190
Testing Efficacy of Vaccines: Parasite Growth

1) Control (Intradermal) N=8

2) ME-TRAP (Intradermal) N=12

3) R21 (Intradermal) N=12

4) R21 (Intravenous) N=5

R21: High efficacy
ME-TRAP: Down select

Days Post Inoculation

Density of Parasites (Determined by PCR)

- Parasites Detected and No Treatment Needed
- Parasites Detected and Treatment Needed
- No Parasites Detected
## Key Outcomes for Vaccine Efficacy Study

<table>
<thead>
<tr>
<th>Parasites Detected by PCR</th>
<th>Threshold for Treatment Reached</th>
<th>Control (ID) n=8</th>
<th>ME-TRAP (ID) N=12</th>
<th>R21 (ID) n=12</th>
<th>R21 (DVI) n=5</th>
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<tr>
<td>No</td>
<td>No</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>9 (75%)</td>
<td>0 (0%)</td>
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<tr>
<td>Yes</td>
<td>No</td>
<td>1 (12.5%)</td>
<td>1 (8.3%)</td>
<td>3 (25.0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>7 (87.5%)</td>
<td>11 (91.7%)</td>
<td>0 (0%)</td>
<td>5 (100%)</td>
</tr>
</tbody>
</table>

- Demonstration of in vivo mechanisms of protection
- R21-induced immunity protects against ID challenge and avoided by IV route
- Synergy between R21-induced and anti-blood stage immunity: i.e., parasites that breakthrough R21-induced immunity mopped up by anti-blood-stage immunity
Summary

❖ Community considerations & consultations in design, introduction, and implementation

❖ Early engagement of Ethics & Regulatory Authorities

❖ CHIM model powerful tool for translational & discovery research
  ✓ Rapid down selection of vaccines
  ✓ Antigen discovery and vaccine development
  ✓ Disease and immune mechanisms
  ✓ Cultural and societal behaviour

Guidelines to include Challenge Studies in Kenya (first issued January 2020)
KEMRI-Wellcome Trust

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Asante sana