Accelerating the development of next generation malaria vaccines through Controlled Human Malaria Infection

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Faces of CHMI-SIKA









CHMI Participants



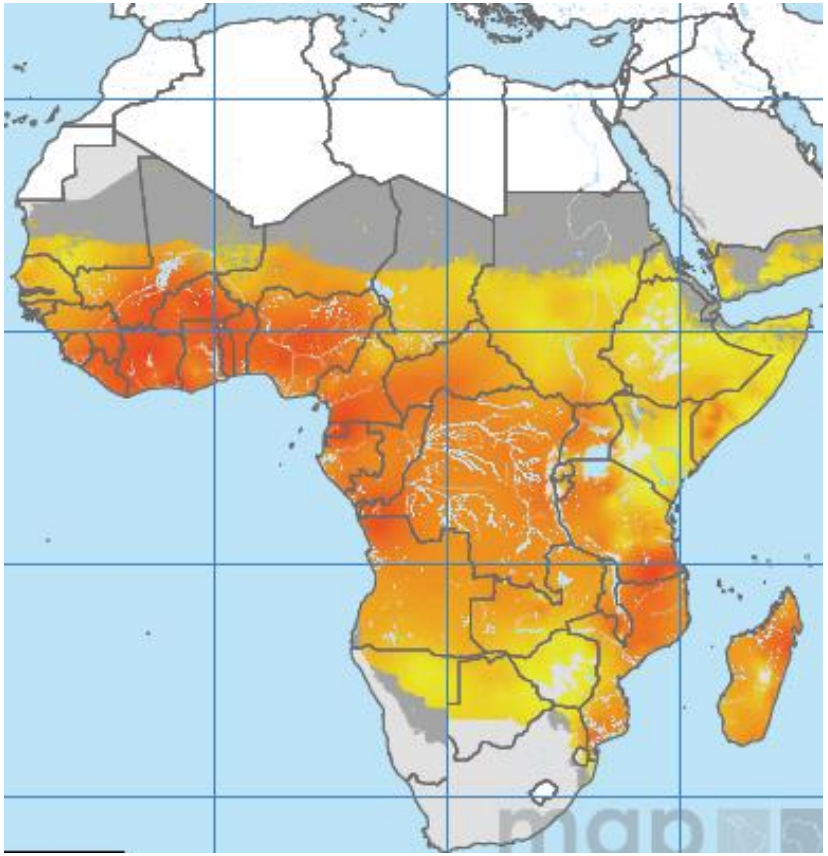






KEMRI | Wellcome Trust

Malaria: 300M episodes per year and 0.6M deaths



Impressive reductions in malaria morbidity and mortality over last 15 years
Substantial disease burden remains, especially in Africa
Vector resistance to insecticides, parasite resistance to drugs

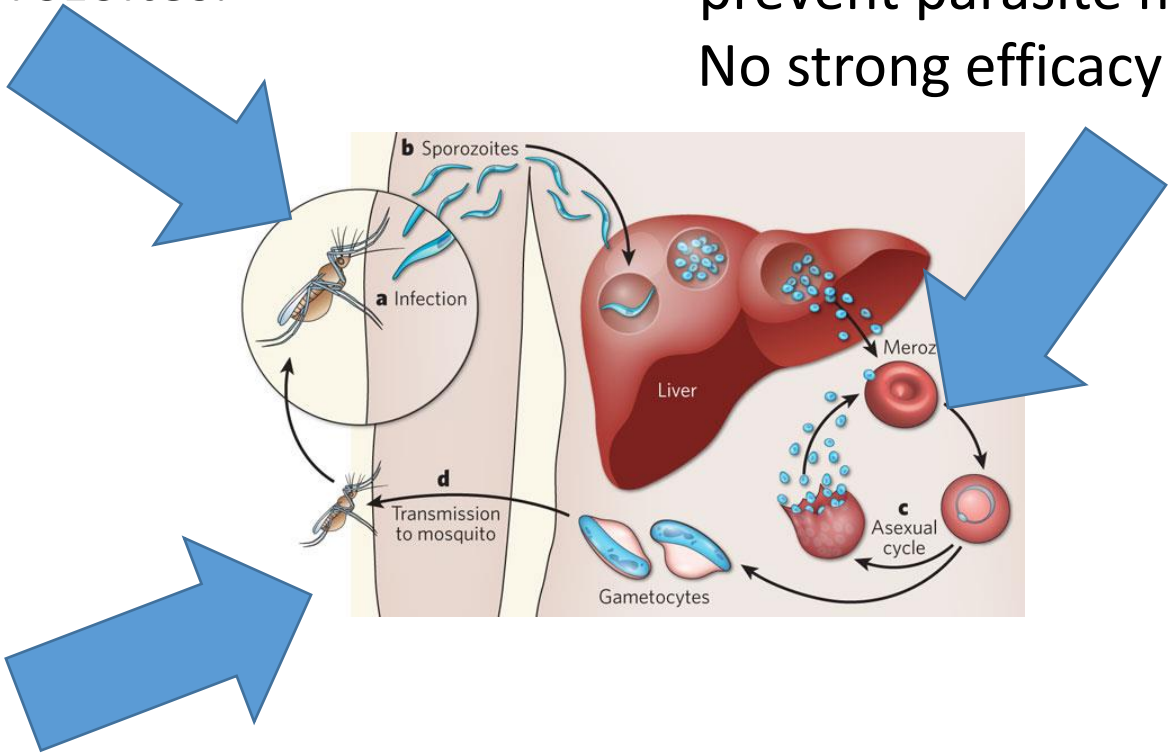
Vaccines development

- RTS,S is current lead vaccine candidate, undergoing implementation trials
- 30% efficacy against malaria, moving to implementation to assess benefit against mortality.
- Sub-unit antigen approach or whole parasite approaches.
- Former requires antigen selection.
- Controlled Human Malaria Infection has been widely used in non-endemic areas to test malaria vaccines prior to field trials.

Multi-Stage Malaria Vaccine

Mosquitoes inject Malaria Sporozoites: e.g. RTS,S, or irradiated sporozoites.

Anti-blood stage component to prevent parasite multiplication. No strong efficacy in field trials.



Malaria taken up by mosquitoes to humans (Anti-Transmission Stage Vaccine)

Current Blocks on the Road Map

Anti-Sporozoite

One Major Antigen on sporozoite coat (Circumsporozoite Antigen)

Proof of principle in controlled human malaria infection

Clinical Trials with 100s of children: 30% efficacy

Anti-blood stage

100s of potential antigens in blood stage

Proof of principle in controlled human malaria infection times 100 antigens not practical.

Clinical Trials with 100s of children not practical without proof of concept

Accelerating Vaccine Development

Anti-Sporozoite

One Major Antigen

Proof of principle in controlled human malaria infection

Clinical Trials with 100s of children: 30% efficacy

Anti-blood stage

Select antigen by study of natural immunity

Proof of principle in controlled human malaria infection

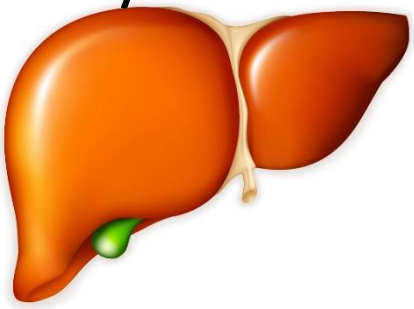
Clinical Trials with 100s of children

Controlled Human Malaria Infection

Day 0: Inject Sporozoites

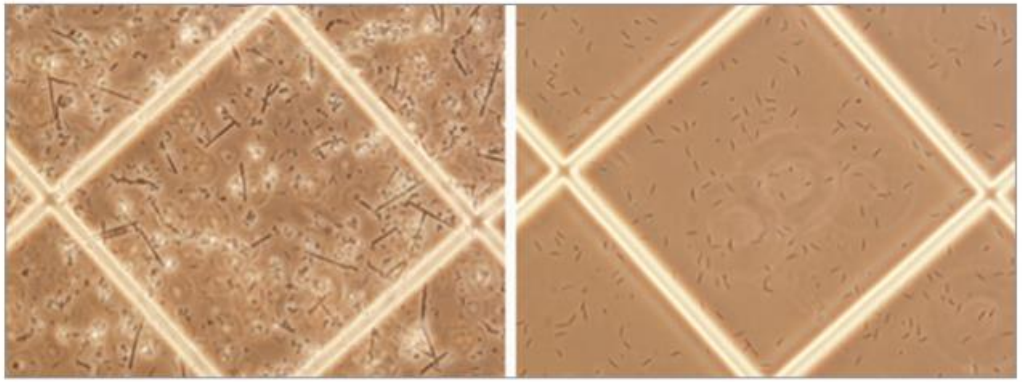
Days 6 onwards: parasites multiply in blood, opposed by immunity.
Use Daily PCR to Measure Quantity of Parasites

Day 0-6: Liver Incubation

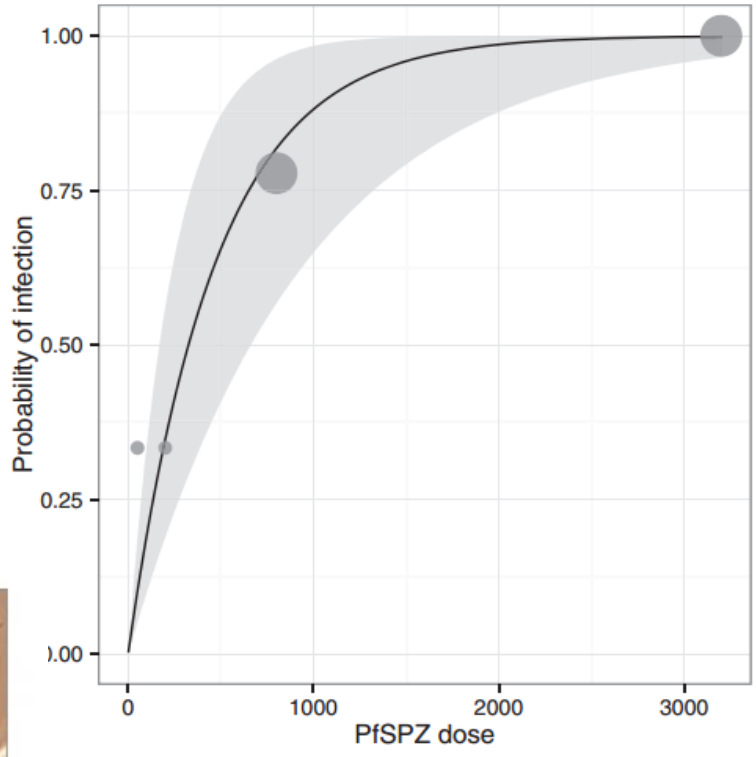


Sanaria: Ability to Produce Cryopreserved Sporozoites in Large Numbers

Sterile Dissection of Mosquito Salivary Glands



Sporozoite purification to remove mosquito material

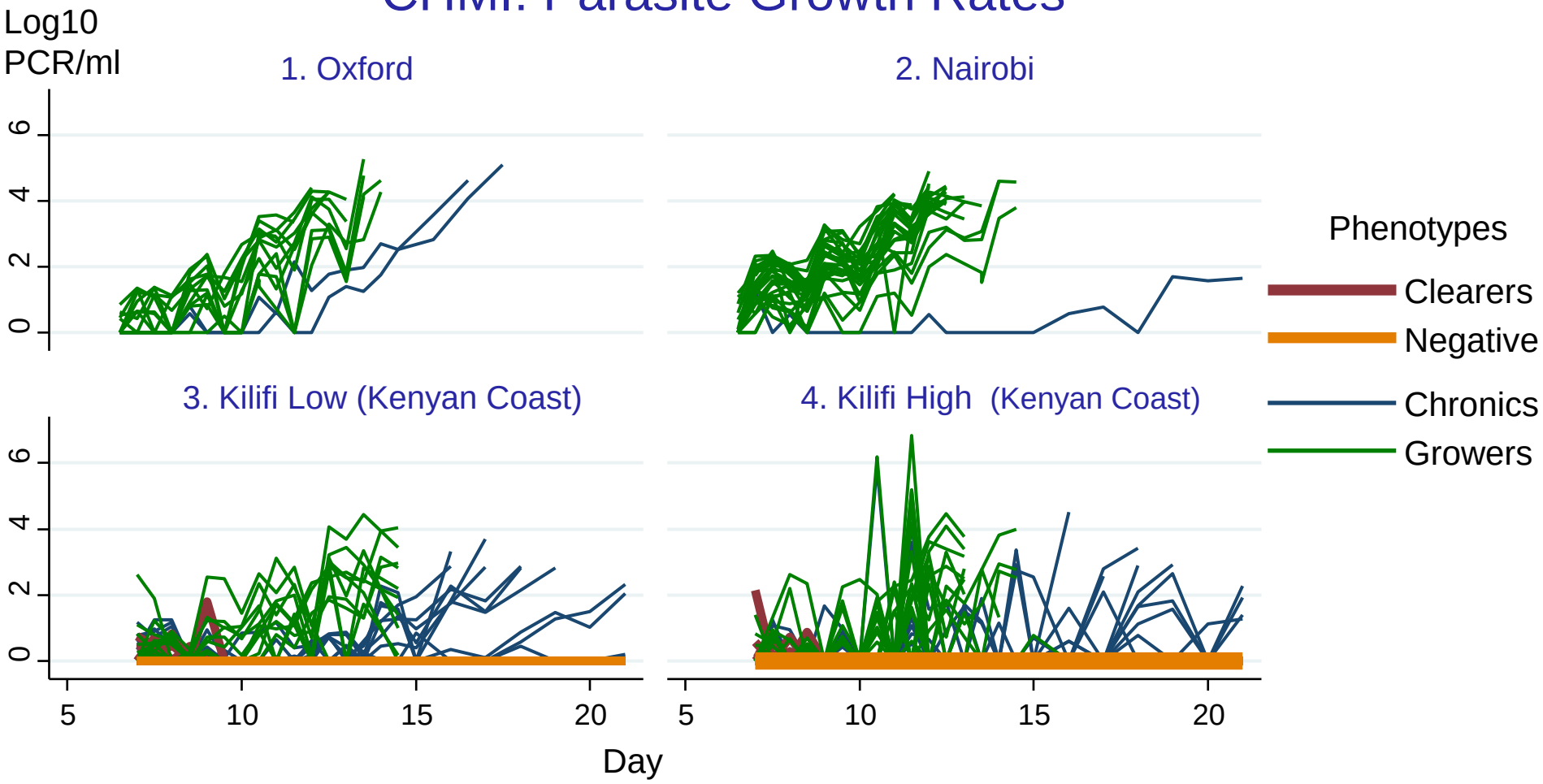


3200 sporozoites reliably infects 100% of non-immune volunteers (Mordmuller et al, 2015)

Objectives

- To measure the correlations between diverse antibody levels and growth rates of P. falciparum in volunteers undergoing CHMI
- Safety of CHMI delivered by DVI in semi-immune volunteers
- **Measure parasite growth rates (the liver-to-blood inoculum) in semi-immune volunteers.**
- Measure the development of immunity to malaria and its effect on the parasite following CHMI in semi-immune volunteers.

CHMI: Parasite Growth Rates



Oxford volunteers show typical non-immune growth rates.
Chronic parasitaemia, parasite clearance or sustained negative results more common at higher endemicity settings.

Next Steps

- Analyse antibody responses to >100 antigens
- Identify which antigen responses are most strongly associated with protection (i.e. Negative throughout > Clearance > Chronic low level > Growth).
- Prioritize those antigens for vaccine development.
- If no evidence of “winning” antigens, then examine if combinations of antigens, or perhaps conclude sub-unit vaccines not plausible if too many.

Conclusion

- CHMI identifies range of host abilities to control parasite growth in Kilifi volunteers.

- Future: New blood stage antigens, data on antibody levels required for protection to target vaccine development for further rapid testing in challenge model.