CHMI – tool for accelerating vaccine development

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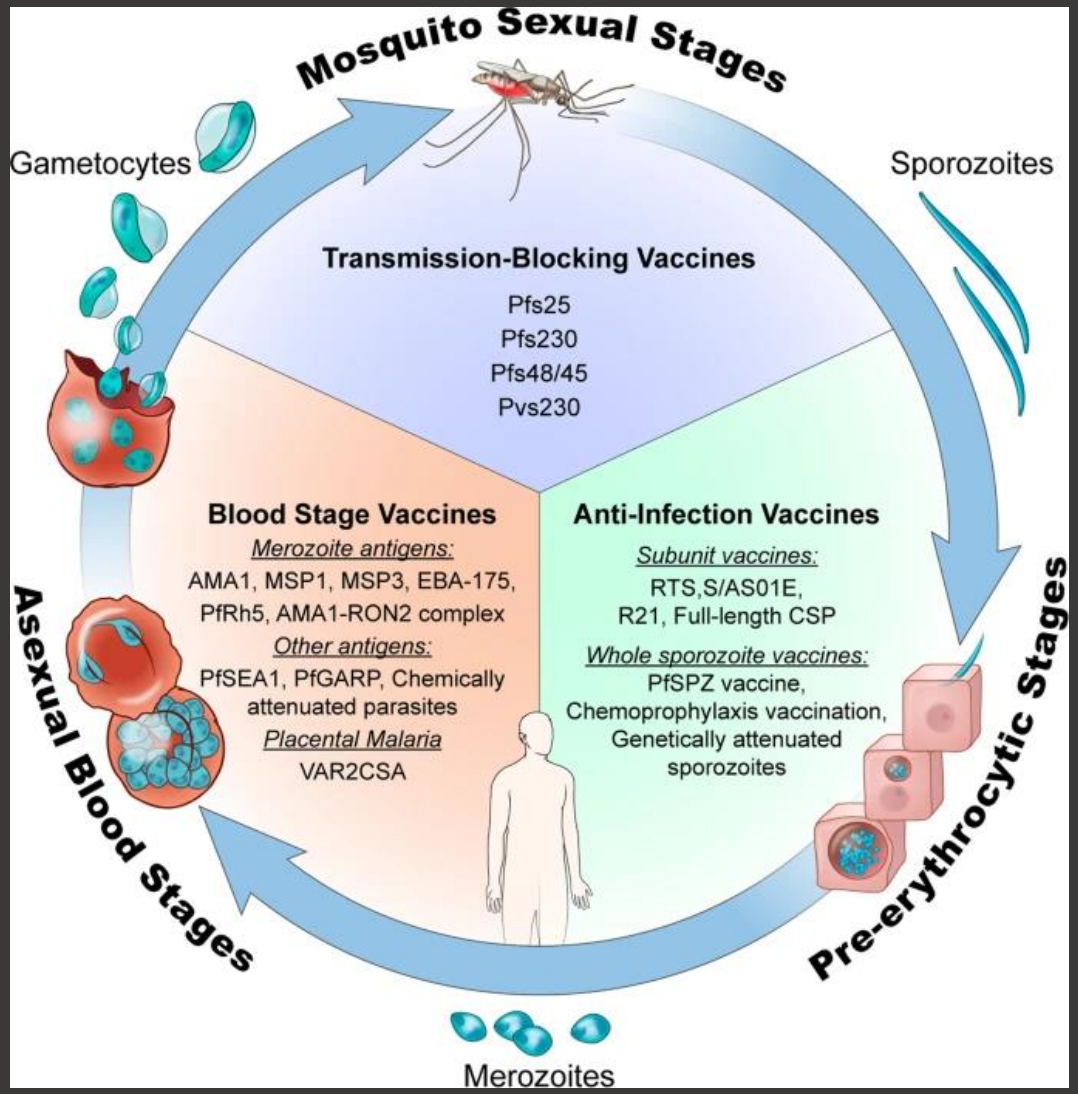
Global Vaccine and Immunisation Research Forum (GVIRF)

Controlled Human Infection (CHI) Models for Vaccine R&D

- What is the current status?
- CHMI in Africa
- Moving forward – work in progress and future developments

Current vaccines in development

Subunit approach requires antigen selection



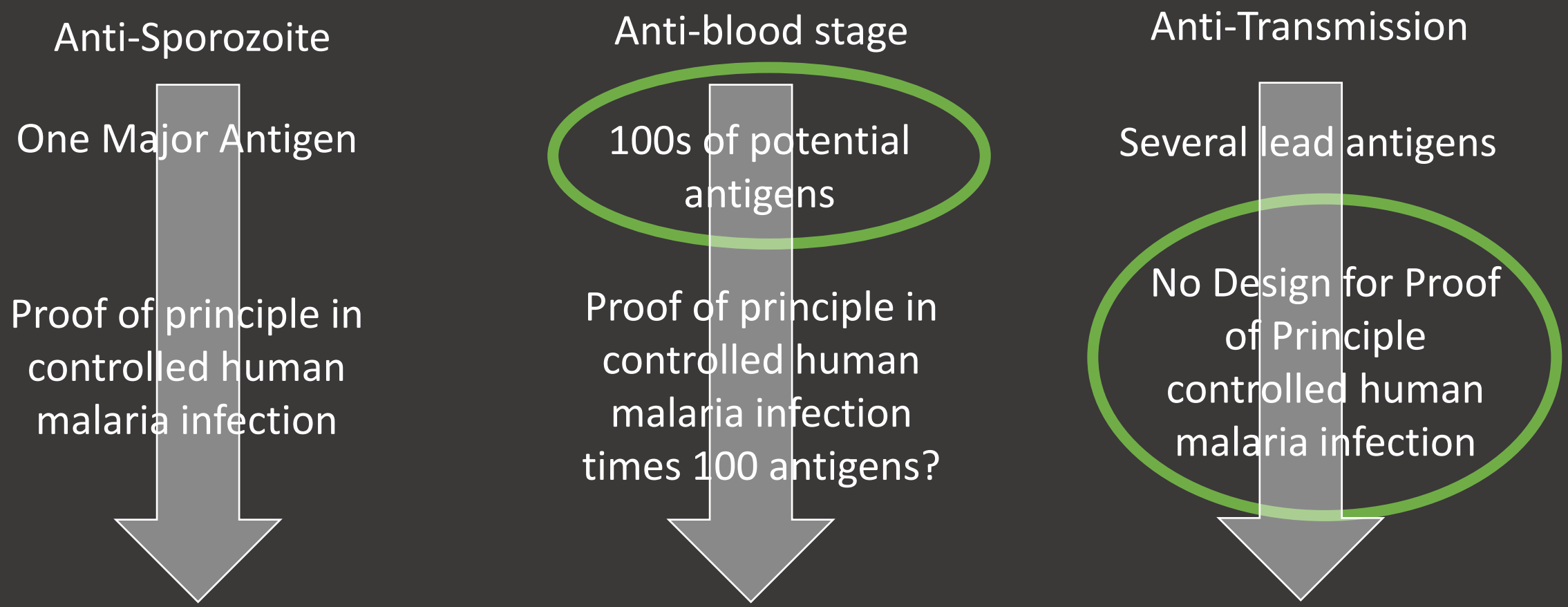
Sub-unit antigen or whole parasite approaches plausible – in various stages of development

434 clinical trials* since 2000

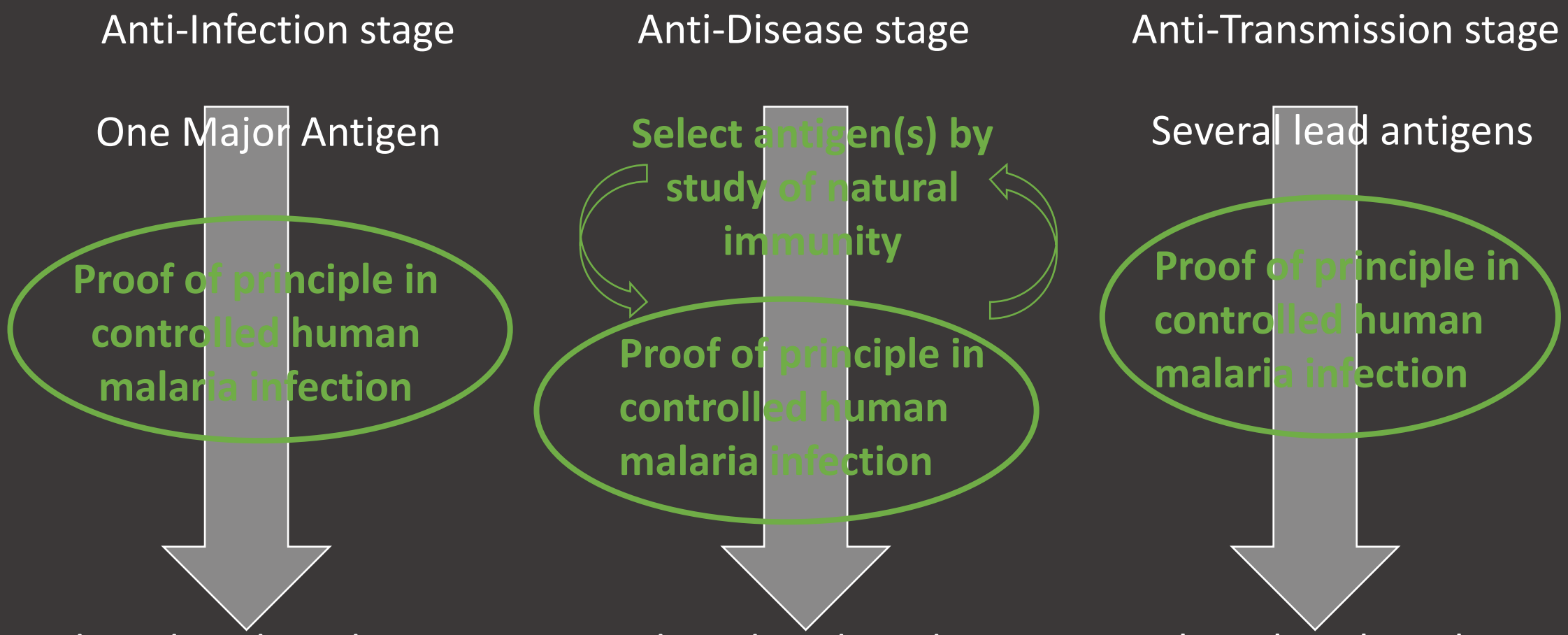
- >40 CHMI studies
- 34 CHMI vaccine studies
  - 31 falciparum, 3 vivax
  - 7 in Africa

Adapted from Duffy and Gorres 2020

Current Blocks on the Road Map



Role of CHMI in Malaria Vaccine Development



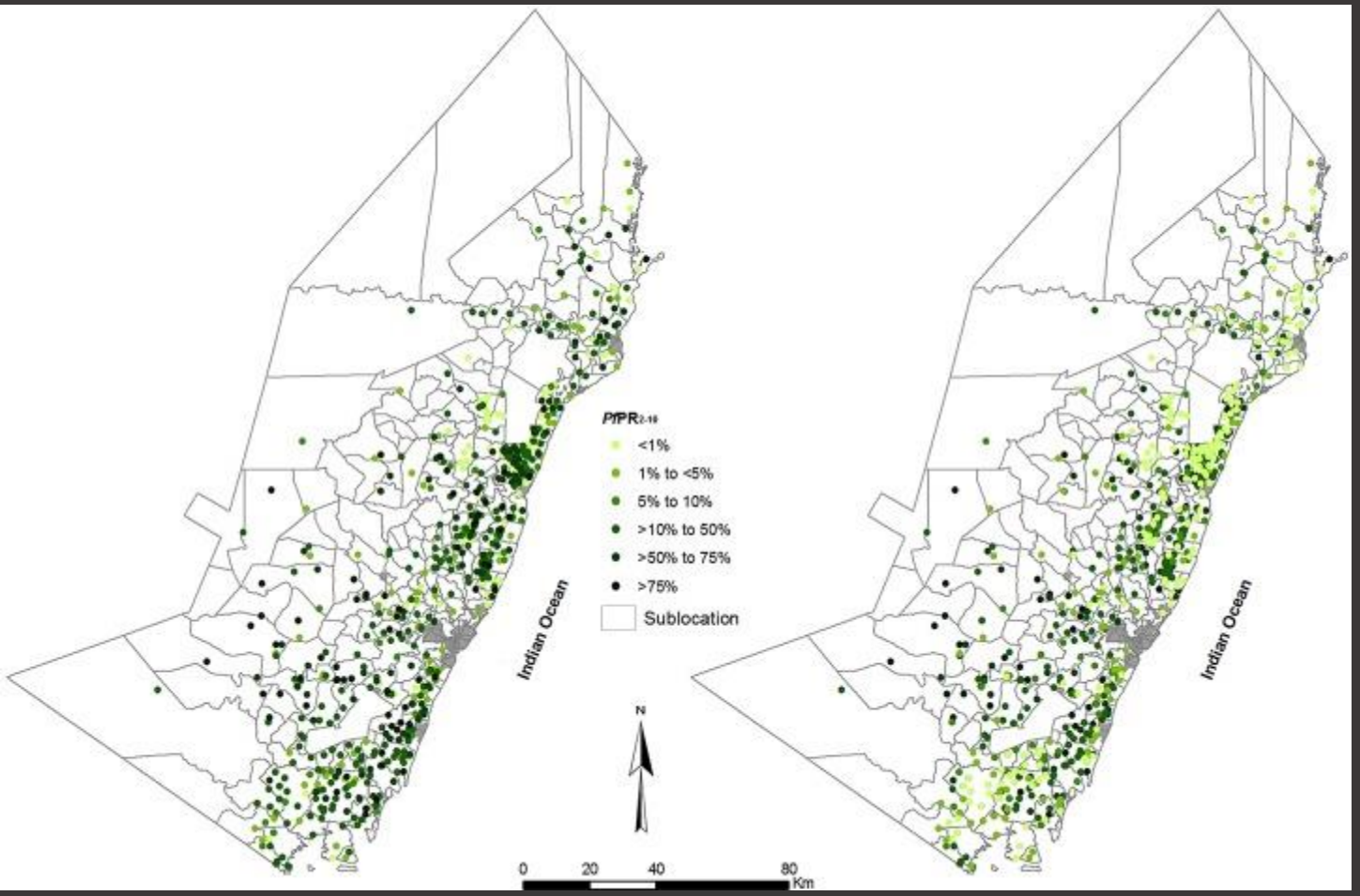
Applications of CHMI

1. Testing vaccine and drug efficacy
2. Serving as the immunogen - PfSPZ-CVac
3. Empowering research institutions in Africa
4. Exploring innate and acquired immunity
5. Generating pivotal efficacy data for licensure (Phase 3)

CHMI widely used in naïve for vaccine efficacy prior to field trials

- Tool to assess naturally acquired immunity (NAI) => down-select potential vaccine candidates
- Test efficacy in the context of NAI

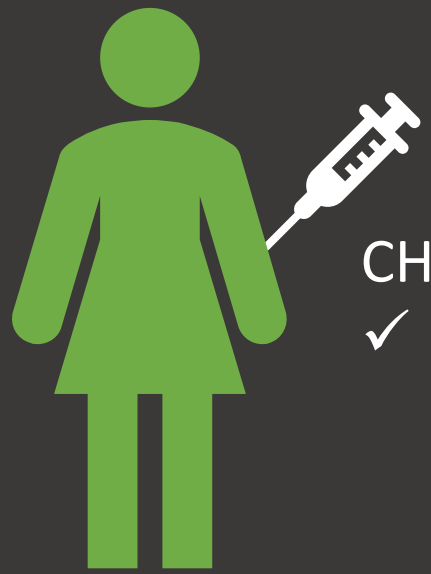
Controlling for variability in exposure



Adapted from Snow et al. 2015

Natural infections:

- ✓ Exposure to vectors variable
- ✓ Unknown parasite doses and genotype



CHMI:

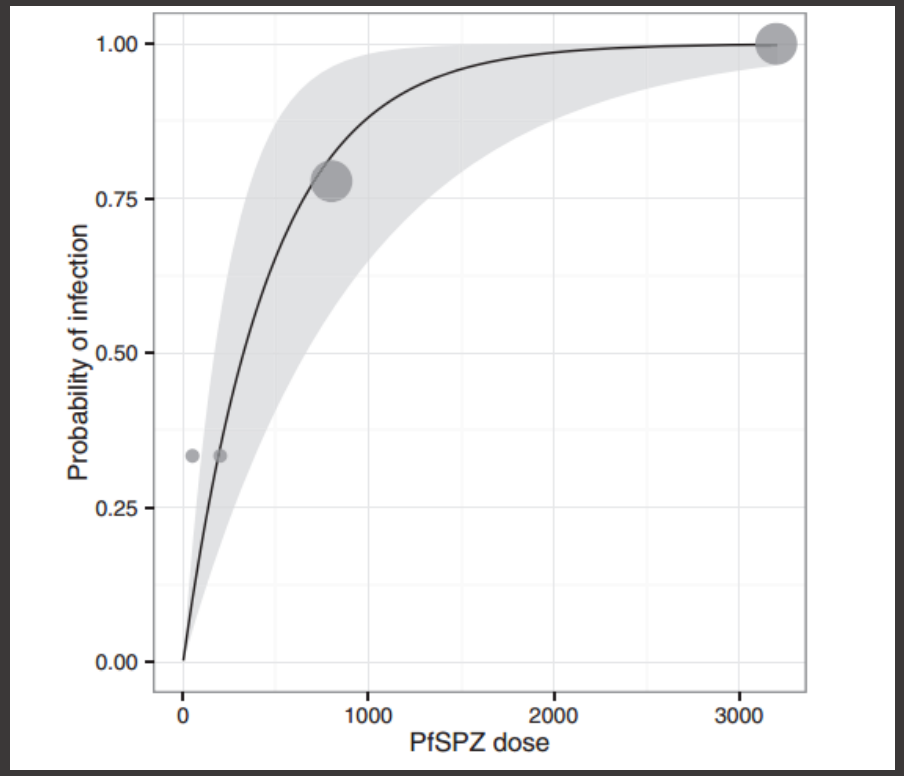
- ✓ Controlled exposure to known dose and genotype

New Process to Produce Cryopreserved Sporozoites in Large Numbers

PfSPZ Challenge for CHMI

Sterile Dissection of Mosquito Salivary Glands

Sporozoite purification to remove mosquito material



Quality Controlled Reliably Infectious Dose (Mordmuller et al, 2015)

>724 Volunteers in 10 Countries undergone CHMI with PfSPZ Challenge since Oct 2010

CHMI in Africa

Africa (falciparum malaria) CHMI Experience

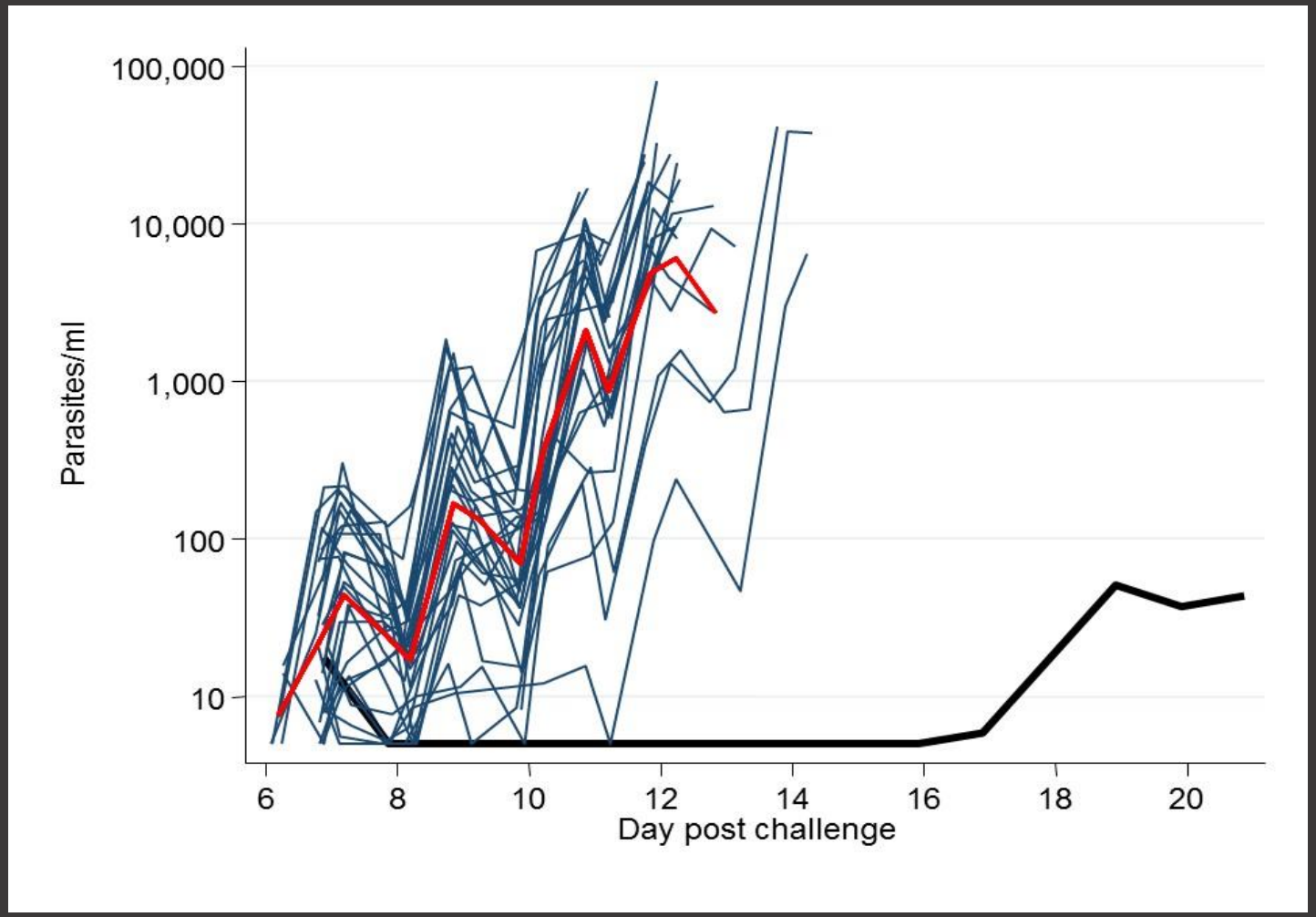
Location	Study Type	Number of Volunteers	Route of Administration	Age (years)	Gender	Malaria Outcome[1]	Reference
Equatorial Guinea	Vaccine efficacy Vaccine efficacy	52 104	DVI DVI	18–35 18–45	Both Both	TBS[2] TBS[2]	NCT02859350 NCT03590340
Gabon	Infectivity Vaccine efficacy	20 12	DVI DVI	18–30 18–40	Both Both	TBS[2] TBS[2]	34 PACTR201503001038304
Gambia	Infectivity	30	DVI	18–35	Males	qPCR	NCT03496454
Kenya	Infectivity[3]	28	IM	18–45	Both	TBS[2]	31
Mali	Vaccine efficacy[4] Vaccine efficacy	62 45	DVI DVI	18–45 18–50	Both Both	TBS[2] TBS[2]	NCT02996695 NCT02627456
Tanzania	Infectivity[3] Vaccine efficacy Vaccine efficacy Vaccine efficacy	24 64 24 18^	ID DVI DVI DVI	20–35 18–35 18–45 18–45	Males Males Both Both	TBS[5] TBS[2] TBS[2] TBS[2]	30 35 NCT02613520 NCT03420053

Adapted from Kapulu et al 2019

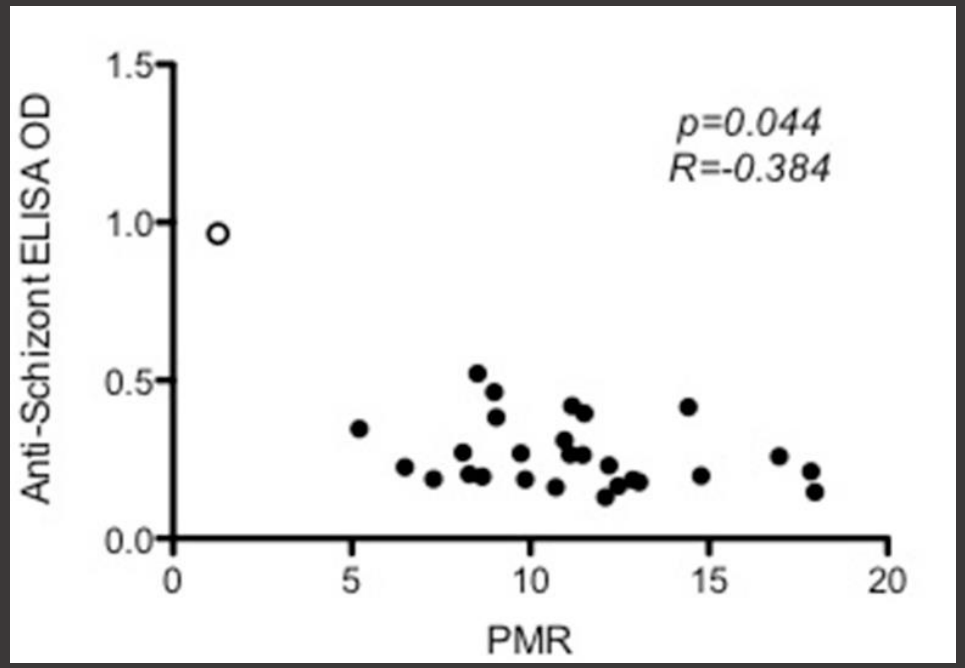
Rationale for Human Infection Studies in Semi-Immune Adults in Kenya

- Understand Acquired Immunity
- Accelerate Vaccine Development
- Test Efficacy of Vaccines (and/or drugs)

Premise for Measuring Immunity *in vivo* in Humans



Proof-of concept challenge study in adults with range of exposures in Kenya

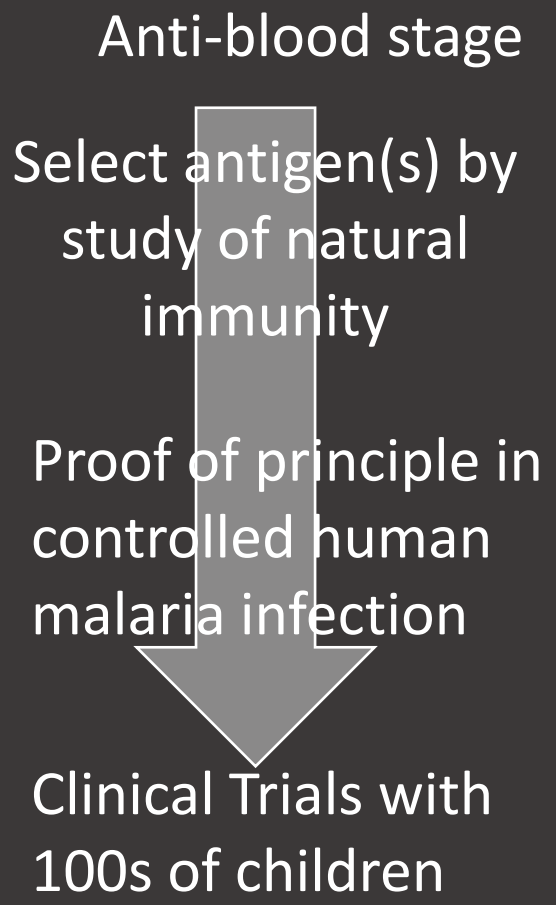


Adapted from Hodgson et al. 2014

Controlled Human Malaria Infection in Semi-Immune Kenyan Adults – CHMI-SIKA

- Understand role of pre-existing immunity in relation to **parasite growth**

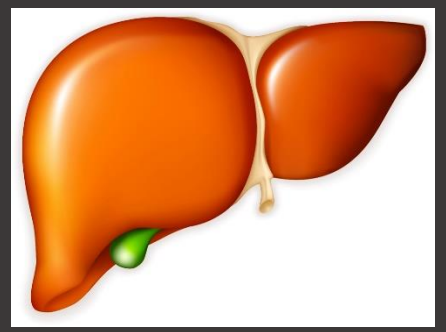
- To identify key **parasite targets** that can be prioritized for vaccine development



Controlled Human Malaria Infection in Kenya

Day 0: Inject Sporozoites

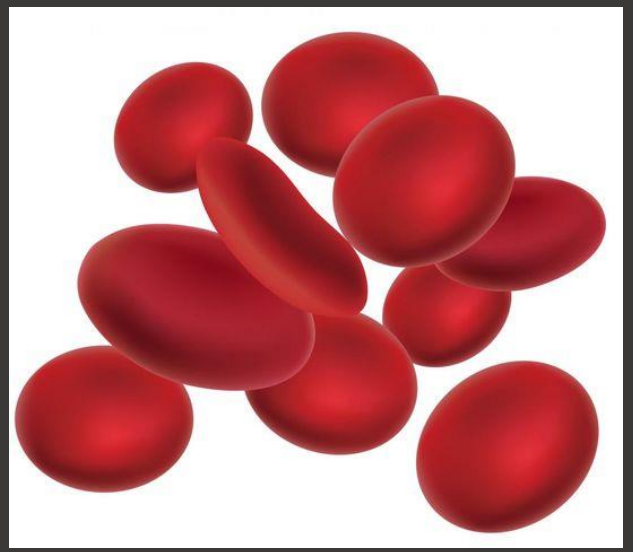
Day 0-6: Liver Incubation



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

Use Daily **qPCR** to quantify parasites

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



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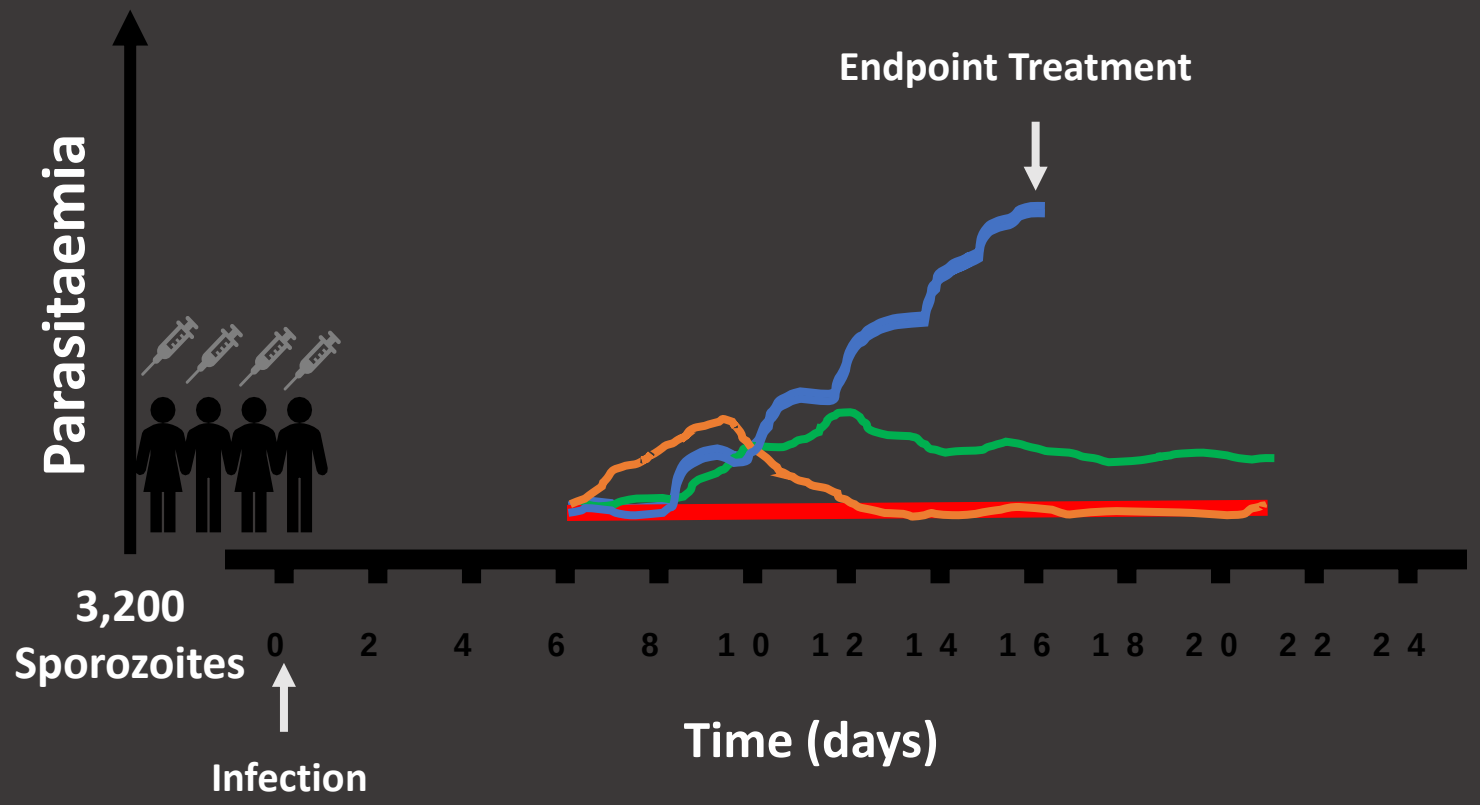
Broad general classification of phenotypes observed



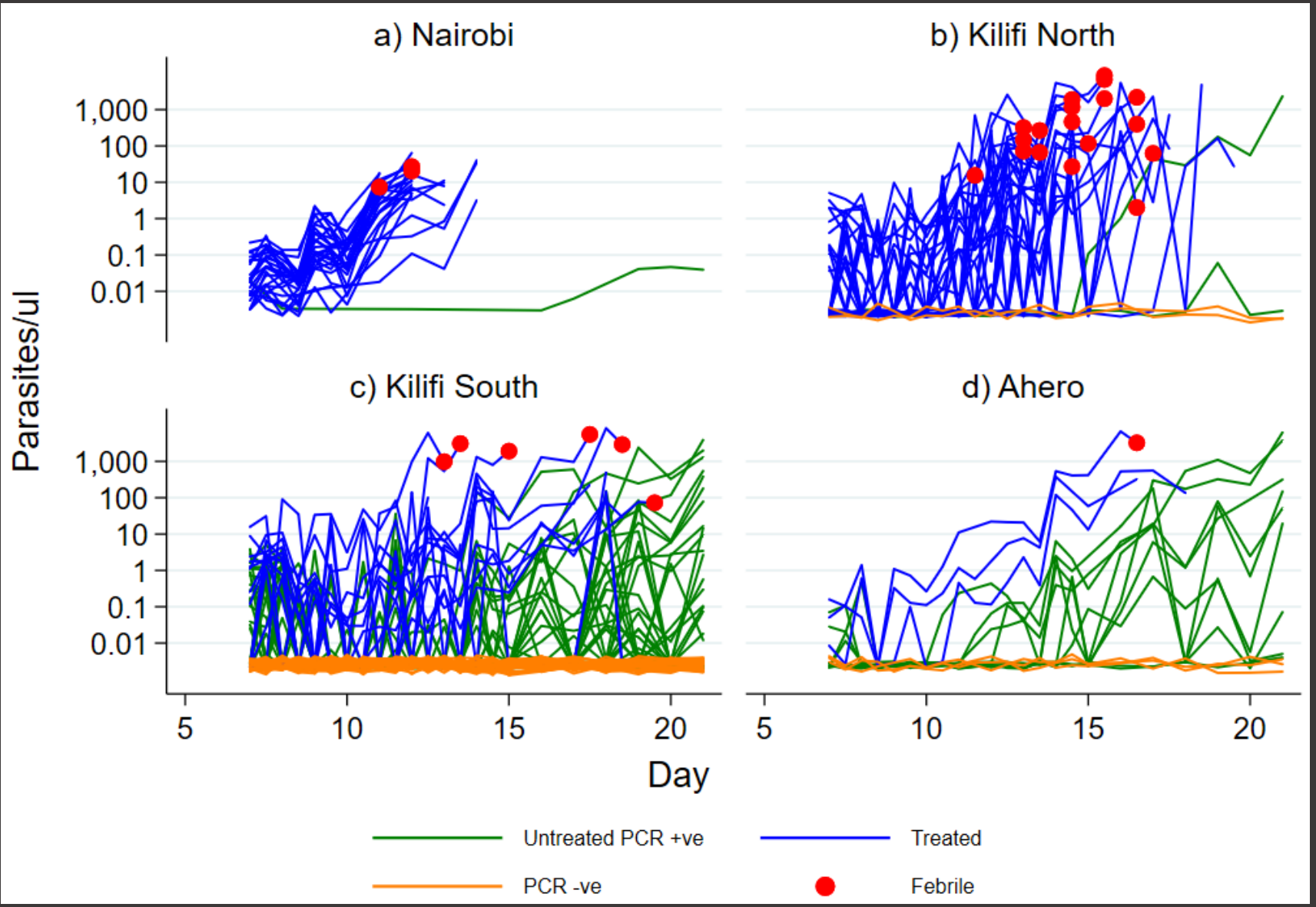
Highly immune Phenotype

Clearance Phenotype

Slow Growth Phenotype

Susceptible Phenotype

Parasite growth in the context of exposure

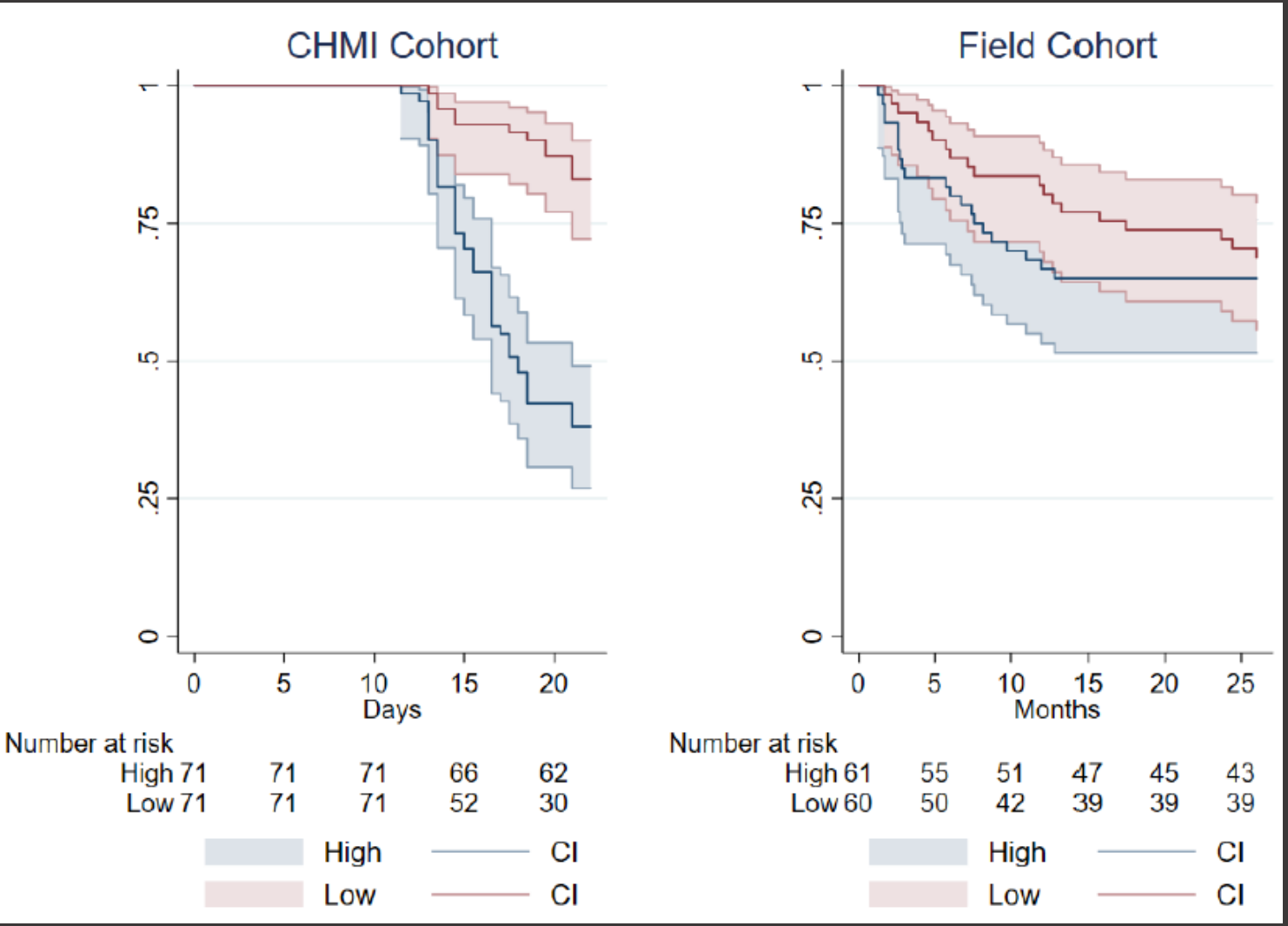


Residence of volunteers has influence on parasite growth & outcome of CHM

- Indication of history of malaria exposure based on location of residence

Adapted from Kapulu et al 2020

Predictive strength of antibody responses



Clear distinction in time to treatment by anti-schizont antibody responses in contrast to field studies based on natural exposure (time to treatment)

CHMI cohort explained 17% of variability in comparison to field cohort studies that explained only 0.8% of the variability in outcome (febrile malaria)

Adapted from Kapulu et al 2020










Work in Progress: Antibody mechanisms

Anti-Merozoite:
- IgG
- IgM
- IgG1
- IgG2
- IgG3
- IgG4

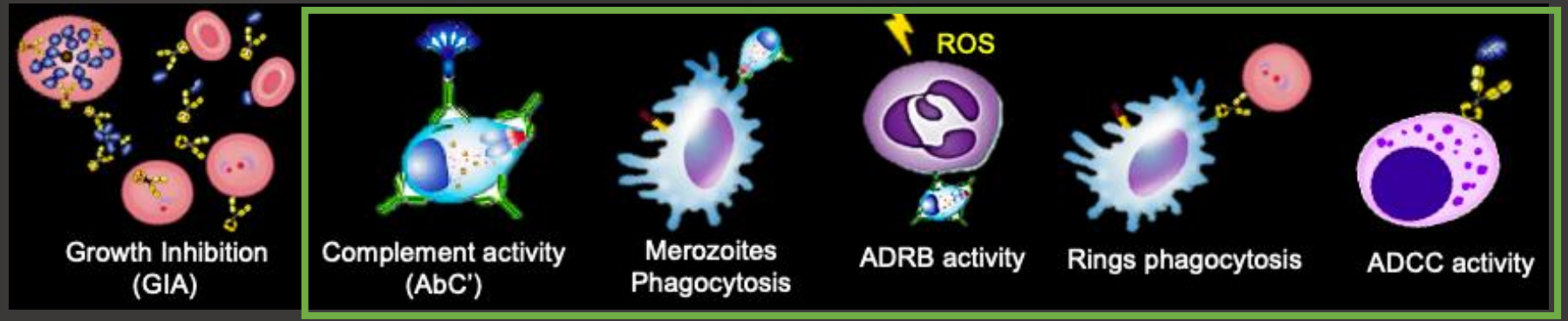
Pre-erythrocytic
- CSP peptide $(NANP)_6C$

Non *P. falciparum* antigens
- Tetanus toxoid

Total antibodies
- Total IgG
- Total IgM

Antibody responses to 76 *P. falciparum* proteins (KILchip ©, Kamuyu *et al* 2018)

❖ Narrowing down to specific antigens as potential vaccine candidates



❖ Fc antibody dependent function is predictive of protection

This project is part of the EDCTP2 programme supported by the European Union

In Summary – Benefits & Gaps

- Parasite growth affected by previous exposure to malaria

CHMI model powerful tool in comparison to field cohort studies in examining correlates of infection

- Evaluate infection doses most suitable for malaria exposed individuals
- For vaccine efficacy studies, requirement to develop models in context of immunity
- Better understand how malaria immunity develops

- Pathogen exposure & modulation of endpoint outcome key for human infection studies in endemic settings

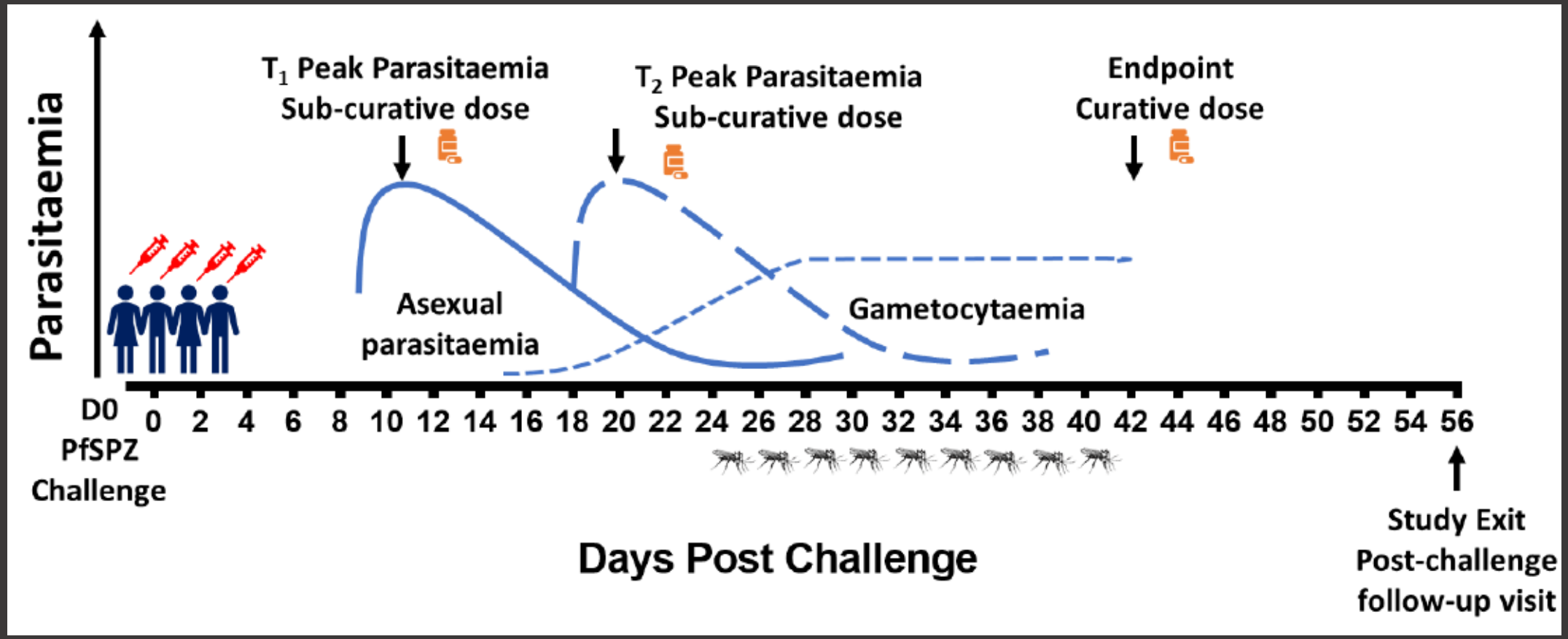
Moving forward – work in progress and future developments

Kenya: Anticipated CHMI Studies

Study features/ Studies	VAC074* (NCT03947190)	CHMI-Transmod* (NCT04280692)
Recruitment sites	Kilifi	Kilifi & Ahero
No. of Pax	64	105
Maximum infecting dose	PfSPZ 3,200 (DVI) or 22,500 (ID)	Dose ranging – PfSPZ 6,400; 12,800; and 25,600 (DVI)
Planned procedures (in order)	• Vaccine administration and enrolment into CHMI – includes control group • Two routes of CHMI	• Injection of sporozoites • Varying doses of sporozoites • Sub-curative anti-malarial treatment • Mosquito feeding assays to assess infectivity
Longest in-patient stay	24 days	45 days
Means of infection	DVI or Intradermal	DVI
Direct therapeutic benefit	Possibility if vaccine(s) work	Nil
Start date	2021	2021

*EDCTP funded study

**Wellcome Trust Funded study


Parasitaemia
T1 Peak Parasitaemia
Sub-curative dose
T2 Peak Parasitaemia
Sub-curative dose
Endpoint
Curative dose
Asexual
parasitaemia
Gametocytaemia
D0
PfSPZ
Challenge
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54 56
Study Exit
Post-challenge
follow-up visit
Days Post Challenge

VAC074 – Phase IIb CHMI

Week	0	4	8	12
Group 1 N=20	R21/ Matrix M 10µg /50µg	R21/ Matrix M 10µg /50µg	R21/ Matrix M 10µg /50µg	CHMI (ID)
Group 2 N=20	ChAd63 ME-TRAP $5x10^{10}$ vp		MVA ME-TRAP $2x10^{8}$ pfu	CHMI (ID)
Group 3 N=10	R21/ Matrix M 10µg /50µg	R21/ Matrix M 10µg /50µg	R21/ Matrix M 10µg /50µg	CHMI (DVI)
Group 4 N=14				CHMI (ID)

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DEVELOPING INNOVATIVE VACCINES

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EDCTP

MMVC Multi-Stage Malaria Vaccine Consortium

Moving forward – work in progress and future developments – *P. vivax*

THE GOAL
Aseptic, Purified, Vialed Cryopreserved *Plasmodium vivax* Sporozoites (PvSPZ) that Meet all Regulatory Standards

Sanaria® PvSPZ Challenge

Fully Infectious PvSPZ for Inoculation

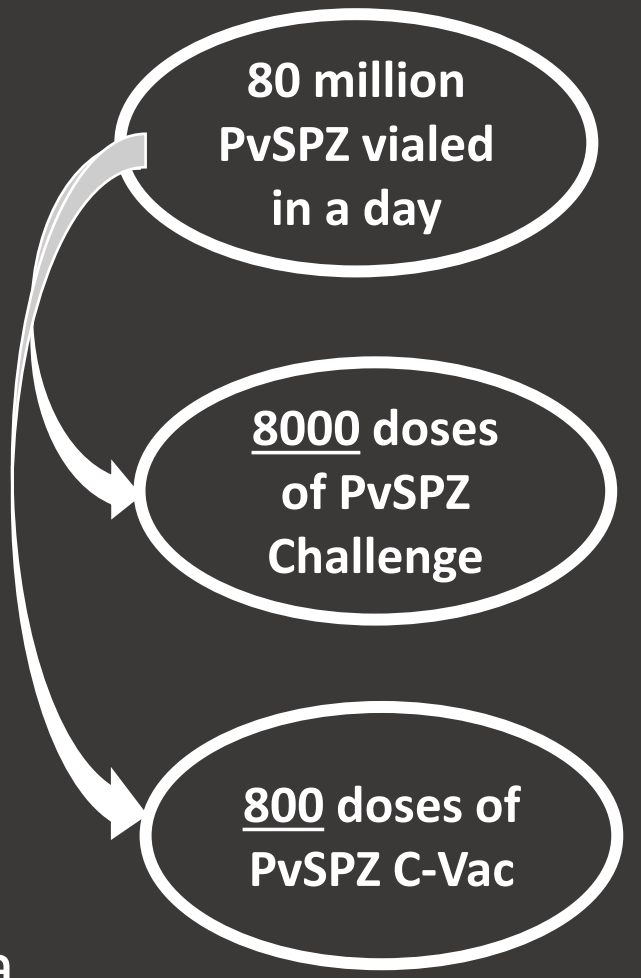
Sanaria® PvSPZ-CVac

PvSPZ Challenge Administered to Volunteers Taking Chemoprophylaxis

Progress towards PvSPZ Challenge – regulatory compliance for human use

In pilot studies with SPF NHPs:

- Asexual and sexual parasitemia profiles of Pv in SPF NHPs were similar to profiles in non-SPF animals from prior studies.
- Aseptic, purified, infectious PvSPZ were generated in aseptic mosquitoes by membrane-feeding Pv-infected blood from the SPF animals.
- In-process asepticity tests were negative for microbial growth.
- PvSPZ products from 2 pilot runs conformed to all in-process, asepticity, *in vitro* potency, and release criteria



Acknowledgements

Study Participants

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Thank you