Controlled Human Malaria Infection Trials (CHMI)

FDA Public Workshop—Clinical Trial Design Considerations for Malaria Drug Development

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Thursday, June 30, 2016

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CHMI Support of Product Development

Target Product Profiles
- Preventive
- **Therapeutic**

Method of infection
- Infected mosquito
- Direct Venous Inoculation

Method of diagnosis
- Nucleic acid tests
- Rapid diagnostics
- Thick blood smear

Method of product administration
- Dose (de)-escalation
- Time-shift
- Vaccine via IV, IM, ID, regimen optimization

Opportunities for discovery
- Protective phenotypes
- Antigen selection

Target Product Profile

Preventive

- Pregnant women and children in endemic settings
- Travelers
- Military
- Post exposure prophylaxis
- Repeat exposures

Therapeutic

- Plasmodia species
- Control of severe disease
- Control of further transmission
- In combination with other drugs
- Concurrent infections

Human Malaria Infection

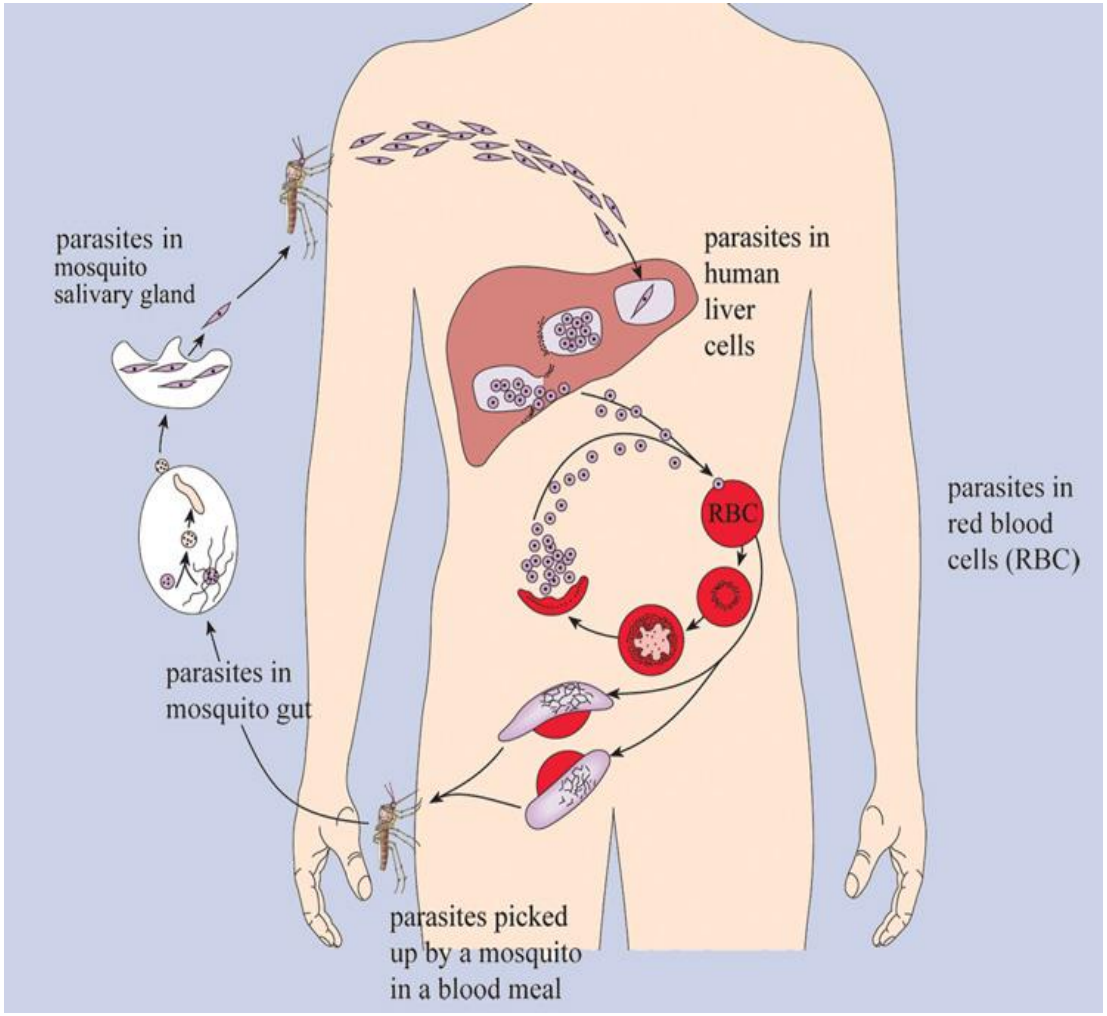


Image from Open Learn Lab Space which was Adapted from: The Open University, 2003, *Infectious Disease*, Book 5: *Evolving Infections*, Figure 3.4)
http://labspace.open.ac.uk/mod/oucontent/view.php?id=439264&extra=thumbnail_id398021309758

Caused by a parasite *Plasmodium*

Five *Plasmodium* species:

- ***P. falciparum***
- ***P. vivax***
- ***P. ovale***
- ***P. malariae***
- ***P. knowlesi***
- ***P. brasilianum***

Complex life cycle with many parasite forms and stages.

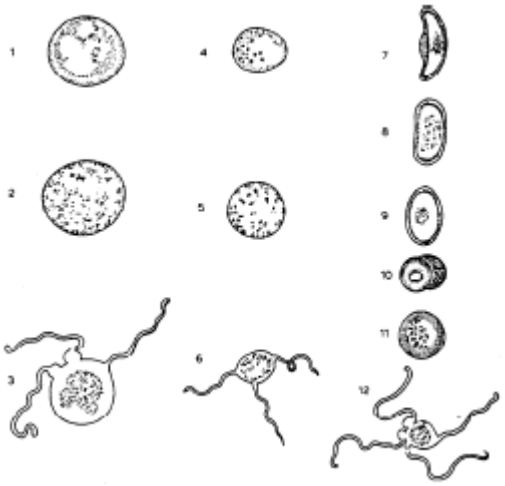
Transmitted by mosquito. Only mosquitoes can spread the parasite to another human.

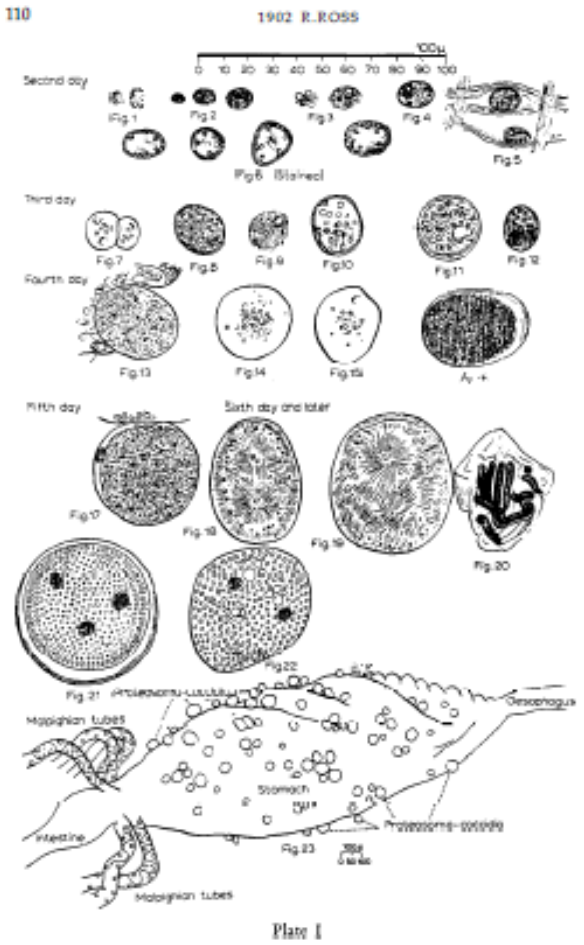
Malaria is not infectious from person to person. You cannot give malaria to someone else.

Breakthroughs for Human Challenge

The Nobel Prize in Physiology or Medicine 1902
Ronald Ross

"for his work on malaria, by which he has shown how it enters the organism and thereby has laid the foundation for successful research on this disease and methods of combating it".





Breakthroughs for Human Challenge

The Nobel Prize in Physiology or Medicine 1927
Julius Wagner-Jauregg

"for his discovery of the therapeutic value of malaria inoculation in the treatment of dementia paralytica"

This discovery led to the testing of patients for syphilis at the former London Asylum that same year using the Wassermann test. In 1921, of 1131 patients tested, slightly over 10% were discovered to have syphilis. The malarial treatment of neurosyphilis was widespread by the 1930s, and continued to be used until the introduction of penicillin in the 1940s.

Treatment for Neurosyphilis / Pf

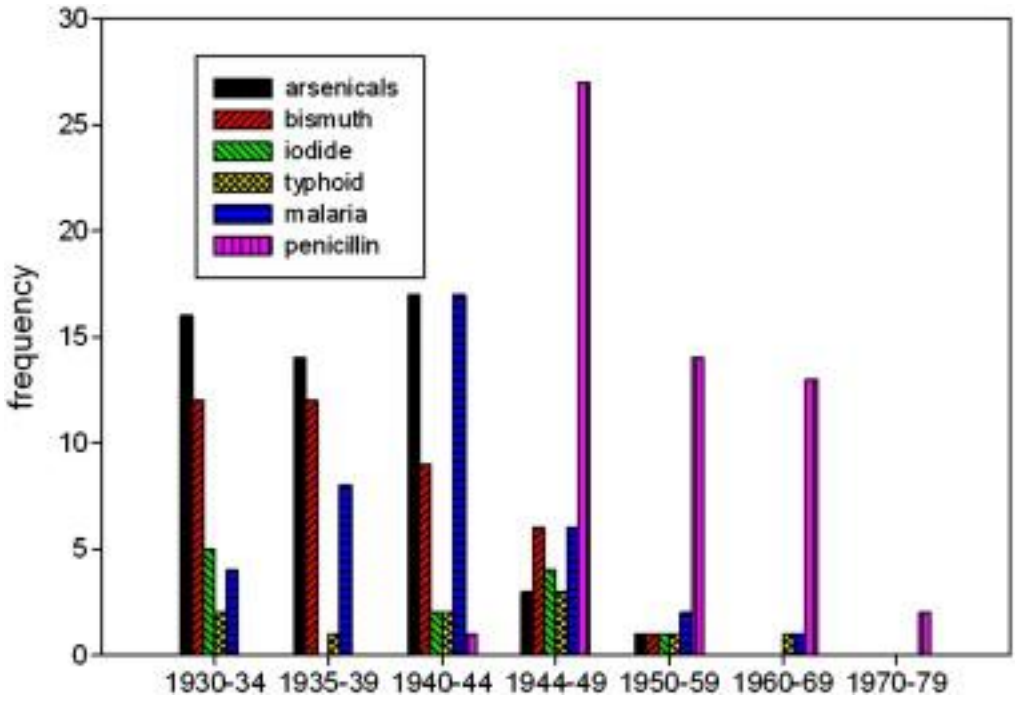


Fig. 1 Year cohorts versus frequency for types of treatment used at the Boston City Hospital.

Diana Patterson , Joel A. Vilensky , Wendy M. Robertson , Joseph Berger

Treatment and diagnostic accuracy of neurosyphilis at Boston City Hospital's Neurological Unit, 1930–1979

Journal of the Neurological Sciences, Volume 314, Issues 1–2, 2012, 1 - 4

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What is CHMI?

Controlled human malaria infection (CHMI) is now used to test vaccines and drugs, as well as to examine physiological and immunological responses to malaria parasites.

- Sporozoite-induced malaria infection (SIM)
  - Via direct venous inoculation
  - Via infected anopheles bites
- Induced blood stage malaria infection (IBSM)

Parameter	SIM		IBSM
	PfSPZ Challenge	Anopheles	
Safety record	3400	>1500	>100
Risk of introduction of adventitious agents	Minimal	Minimal	Possible
Ability to vary size of inoculum	+++	+	+++
Knowledge of size of inoculum	+++	+/–	+++
Logistical ease	LN2, transport, DVI	Need for insectary	Cryopreserved blood
Availability	Sanaria	Widespread	Limited
Life cycle stages amenable to study	All human stages	All human stages	Limited to erythrocytic and gametocytes

Table adapted from Engwerda CR, Minigo G, Amante FH, McCarthy JS. Experimentally induced blood stage malaria infection as a tool for clinical research. Trends Parasitol. 2012 Nov;28(11):515-21.

Methods of Sporozoite-Induced Malaria Infection

Pf Infected Mosquito bite

- Pro
  - Natural route
  - The 'gold standard'
  - Contains the dermal interactions between parasite and people
- Con
  - More expensive
  - Local reactogenicity
  - Implementation challenges
  - Requires a BSL2 insectary
  - Variation in biting behavior
  - May differ when applied to persons from endemic regions

Pf SPZ via Direct Venous Inoculation

- Pro
  - Easier implementation
  - Lower cost
  - More consistent infectious dose?
  - Can achieve same pre-patent period as mosquito bite CHMI
  - No insectary needed
- Con
  - Bypasses the skin immune system
  - Could miss effects of skin-concentrated drugs
  - May or may not be a suitable surrogate of natural infection
  - Many sporozoites are not viable

Mosquito Infection

Mosquito cups enter challenge room through pass through

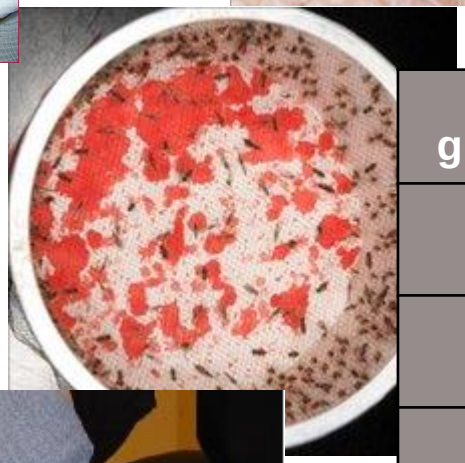
Mosquitoes returned to CeMPMIR post feeding

- Assessed for:
  - Presence of bloodmeal
  - Dissected and assessed for sporozoites
  - Rated using standard 0, 1+,2+,3+,4+ rating

Results recorded on challenge form

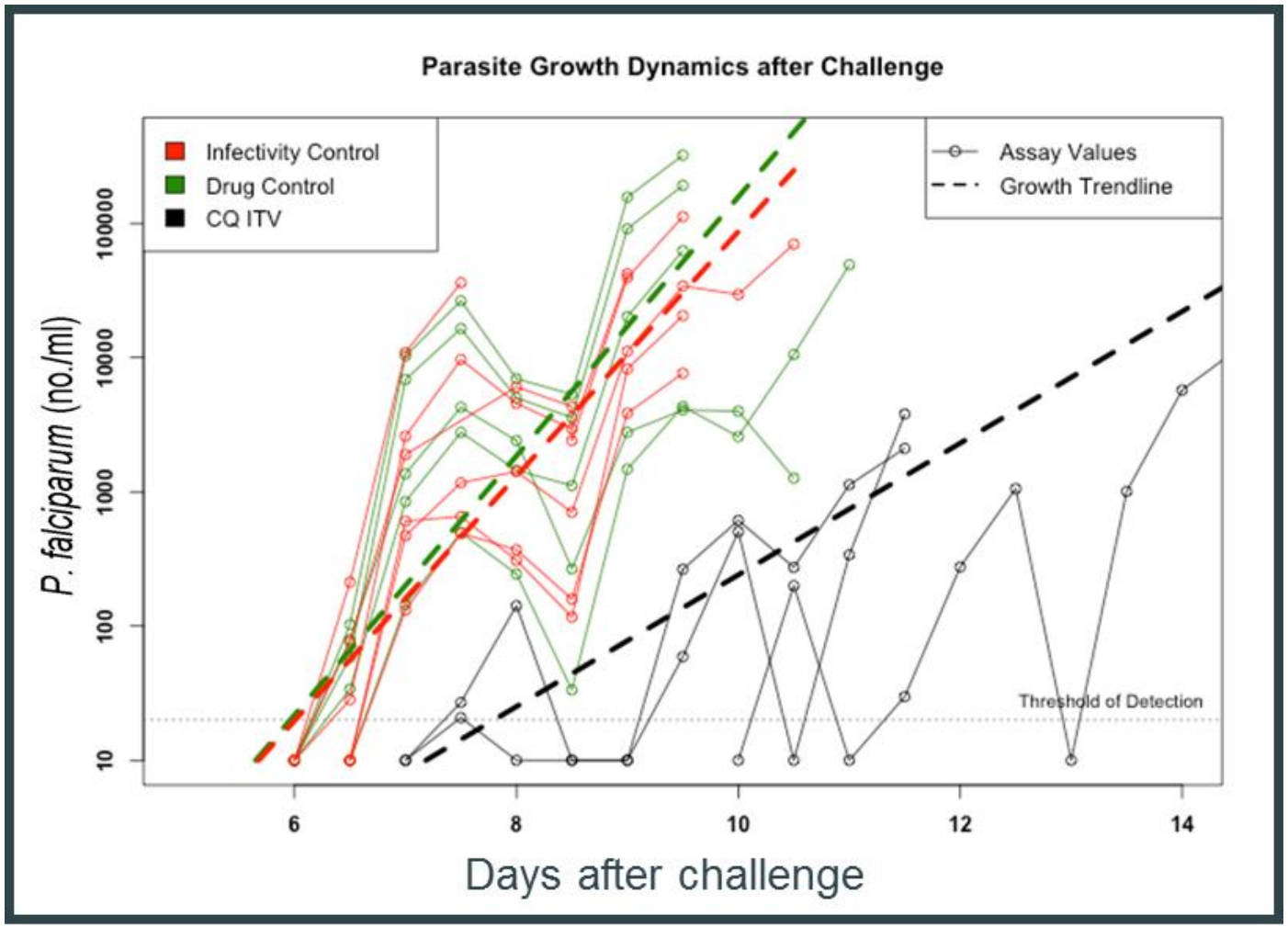
Repeat until 5 infected bites at ≥2+ rating achieved

Malaria Challenge



Salivary gland score	Approximate number of sporozoites
0	no sporozoites observed
+1	1-10 sporozoites observed
+2	11-100 sporozoites observed
+3	101-1000 sporozoites observed
+4	>1000 sporozoites observed

Mosquito Challenge SIM Kinetics



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Healy SA, et al. Infection-Treatment-Vaccination to Prevent *Plasmodium falciparum* Malaria Infection. ASTMH, 2014.

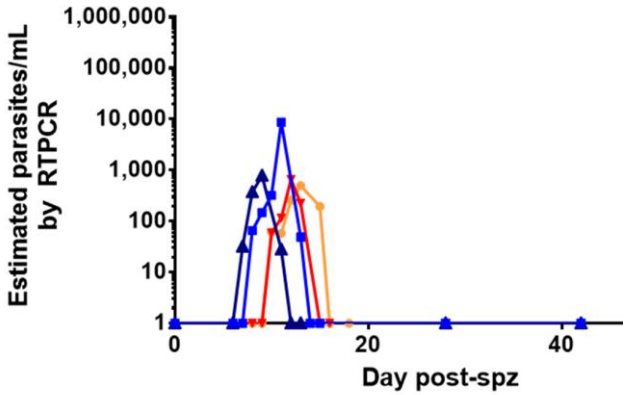
Malaria Challenge via DVI

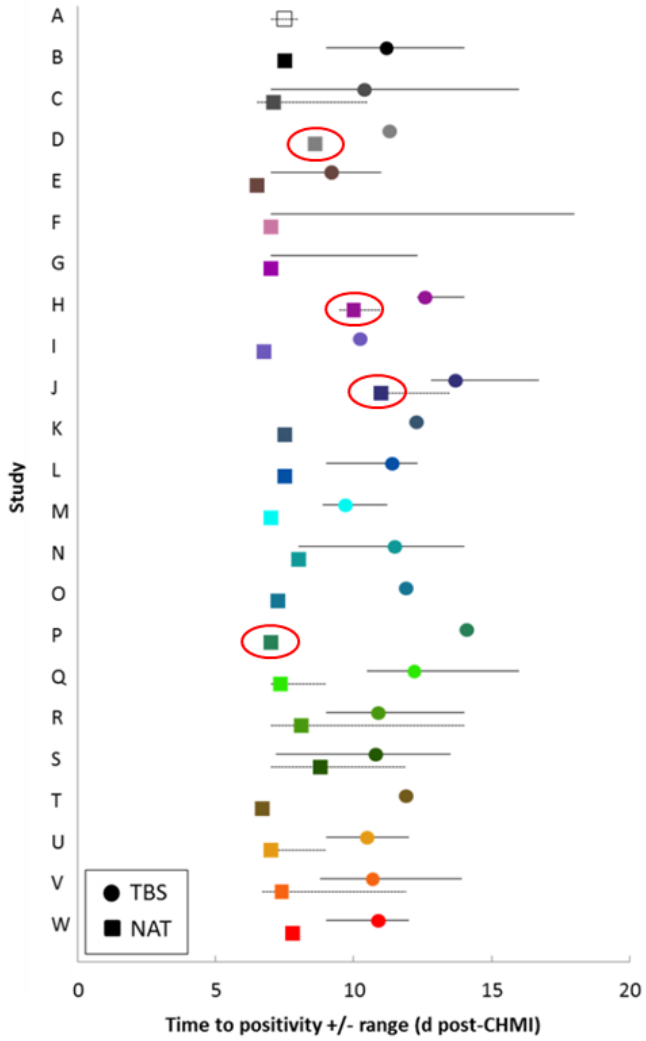
- Thaw of PfSPZ from LN2 and dilution in PBS
- Direct venous inoculation via tuberculin syringe

PfSPZ Challenge SIM Kinetics

All are Pf Mos except:

- D: DVI PfSPZ
- H: ID PfSPZ
- J: ID PfSPZ
- P: IM PfSPZ





CHMI va IBSM

- Evaluation of the parasitaemia of the P. falciparum red blood cell banks
  - 78%
  - 1.5 – 4.5% rings
- Confirmation of the identity
- Evaluation of the viability
  - P. falciparum 7G8 – 15%
  - P. falciparum NF54 – 50%
- Mycoplasma, endotoxin and viral testing
- Identity testing
- In vitro anti-malaria drug susceptibility
- Quality review

Stanisic *et al. Malaria Journal* (2015) 14:143
DOI 10.1186/s12936-015-0663-x

MALARIA JOURNAL

METHODOLOGY Open Access

Development of cultured *Plasmodium falciparum* blood-stage malaria cell banks for early phase *in vivo* clinical trial assessment of anti-malaria drugs and vaccines

Danielle I Stanisic[1*], Xue Q Liu[1], Sai Lata De[1], Michael R Batzloff[1], Tanya Forbes[1], Christopher B Davis[1], Silvana Sekuloski[2], Marina Chavchich[3], Wendy Chung[2], Katharine Trenholme[2], James S McCarthy[2], Tao Li[4], B Kim Lee Sim[4], Stephen L Hoffman[4] and Michael F Good[1*]

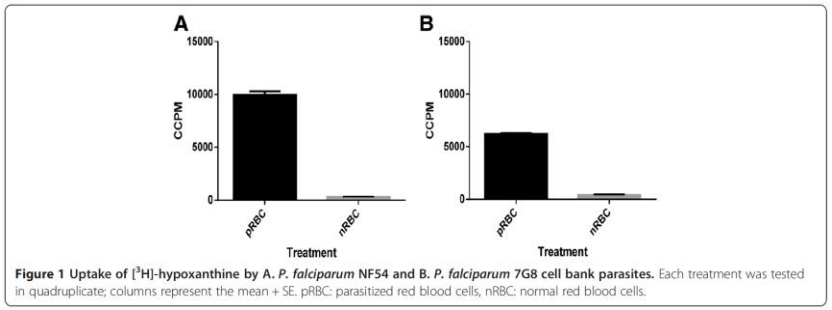
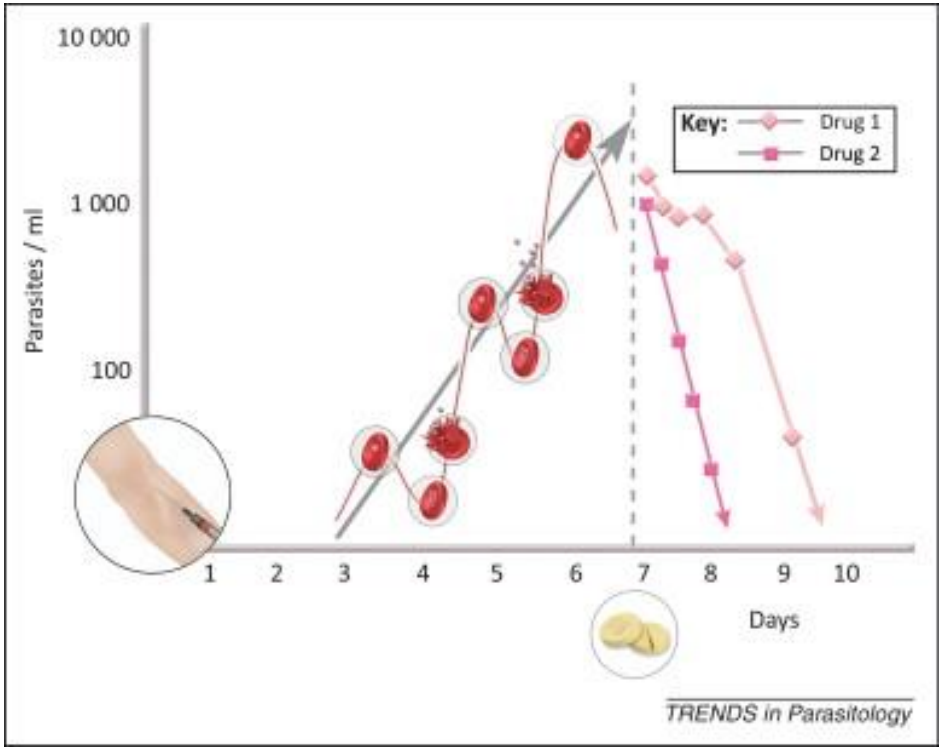


Figure 1 Uptake of [^{3}H]-hypoxanthine by A. *P. falciparum* NF54 and B. *P. falciparum* 7G8 cell bank parasites. Each treatment was tested in quadruplicate; columns represent the mean + SE. pRBC: parasitized red blood cells, nRBC: normal red blood cells.

IBSM Growth Kinetics



Schematic diagram of the course of induced blood stage malaria infection in human volunteers. Parasite counts are typically measured by qPCR following in vivo inoculation with ~1800 infected red cells containing viable ring stage parasites.

Christian R. Engwerda , Gabriela Minigo , Fiona H. Amante , James S. McCarthy. Experimentally induced blood stage malaria infection as a tool for clinical research. Trends in Parasitology, Volume 28, Issue 11, 2012, 515 – 521.

Methods of Malaria Diagnosis

Characteristic	RDT	Thin BS	Thick BS	LAMP	PCR	RT-PCR
LoD (1000s para/μL)	100+	100+	5-10	1	0.02	0.02
Volume (μL)	30-50	1-2	5	30	500	50
Turnaround time (hr)	<0.5	<1	<12	1-2	6-24	6-24
High-throughput	-	-	-	+	+	+
Point-of-care	+	-	-	+/-	-	-
Internal control	+	-	-	-	+/-	+
Useful* pooling	-	-	-	+	-	+
Species ID	+	+	-	+**	+	+
Gametocytes	-	+	+	-	-	+
'One-tube' multiplex	+	-	-	-	+	+
Cost	$$	$	$	$-$$	$$$	$$$

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LoD, limit of detection; *LoD < 1 parasite/μL; **Requires multiple tubes

Diagnosis vs. Clinical Symptoms

Prepatent Period (days)

- Mean: 11.2
- Median: 11.0
- Range: 9-14

Incubation Period (days)

- Mean: 9.7
- Median: 9.5
- Range: 6-14

Onset of symptoms

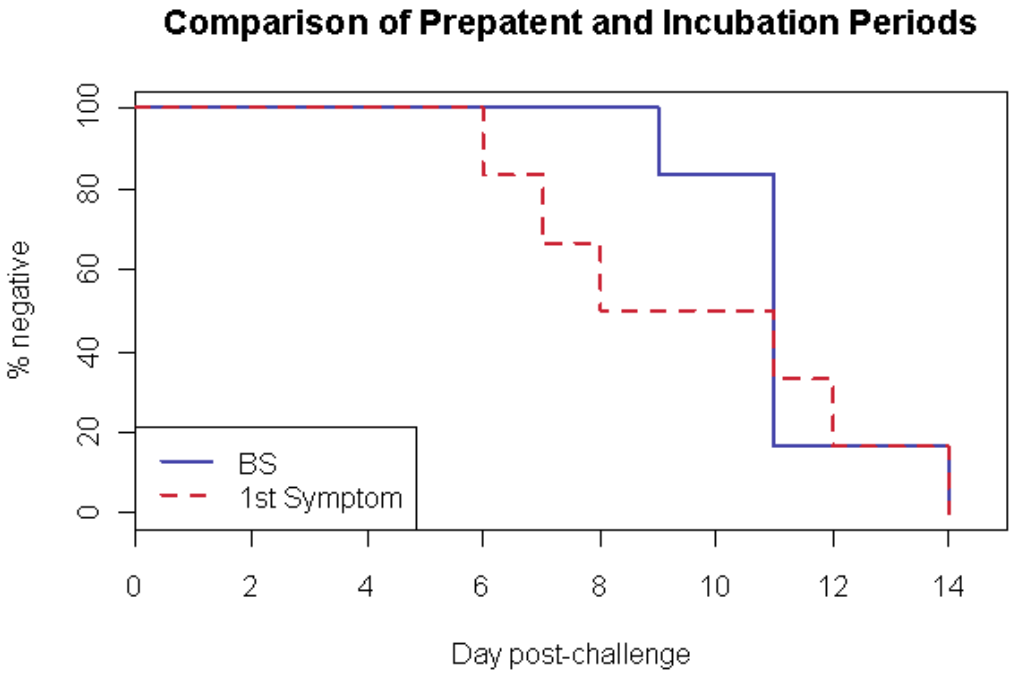
- Prior to 1st + BS: 3 (50%)
- Day of 1st +BS: 2 (33.3%)
- After 1st +BS: 1 (16.7%)

OPEN ACCESS Freely available online

PLOS ONE

Safety and Comparability of Controlled Human *Plasmodium falciparum* Infection by Mosquito Bite in Malaria-Naïve Subjects at a New Facility for Sporozoite Challenge

Angela K. Talley[1], Sara A. Healy[2], Olivia C. Finney[1], Sean C. Murphy[3], James Kublin[4], Carola J. Salas[5], Susan Lundebjerg[1], Peter Gilbert[4], Wesley C. Van Voorhis[6], John Whisler[1], Ruobing Wang[1], Chris F. Ockenhouse[7], D. Gray Heppner[7], Stefan H. Kappe[1], Patrick E. Duffy[2]*



Product Administration vis a vis CHMI

Preventive/prophylaxis studies

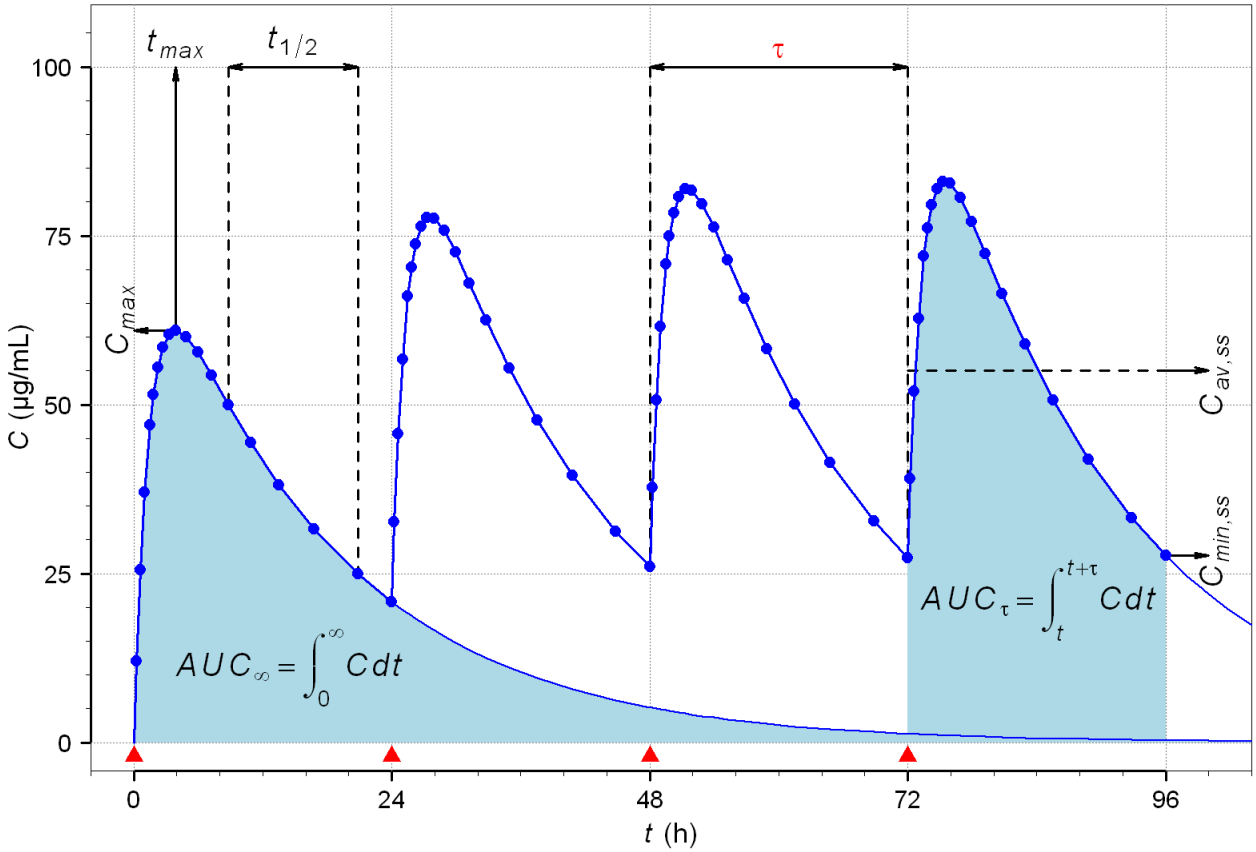
- Time-shift of single administration at a fixed dose prior to CHMI
  - Provides more precision for PK/PD
- Dose de-escalation at a fixed time (or narrow window) prior to CHMI
  - Very informative for further development
- Multiple dose, multiple CHMI
  - Representative of the field

Therapeutic studies

- Dose escalation/de-escalation
- Diagnostic threshold
- Timing of rescue therapy
- Intermittent presumptive therapy
- Combination therapy
- Impact of coinfection on antimicrobial chemotherapy and drug resistance

Method of Product Administration

Drugs – Pharmacokinetics



Liberation - release

Absorption - entering the blood circulation.

Distribution - dispersion throughout the body.

Metabolization (or biotransformation, or inactivation) – transformation of parent compounds into daughter metabolites.

Excretion

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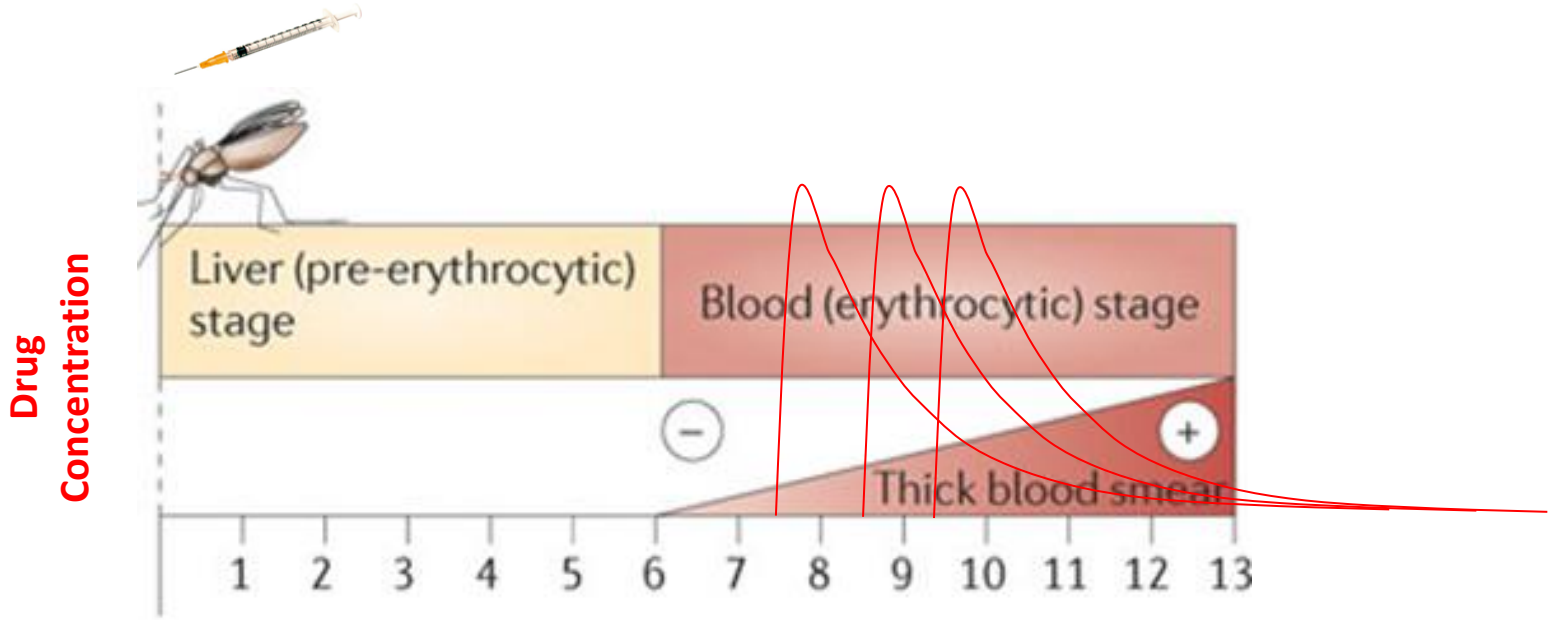
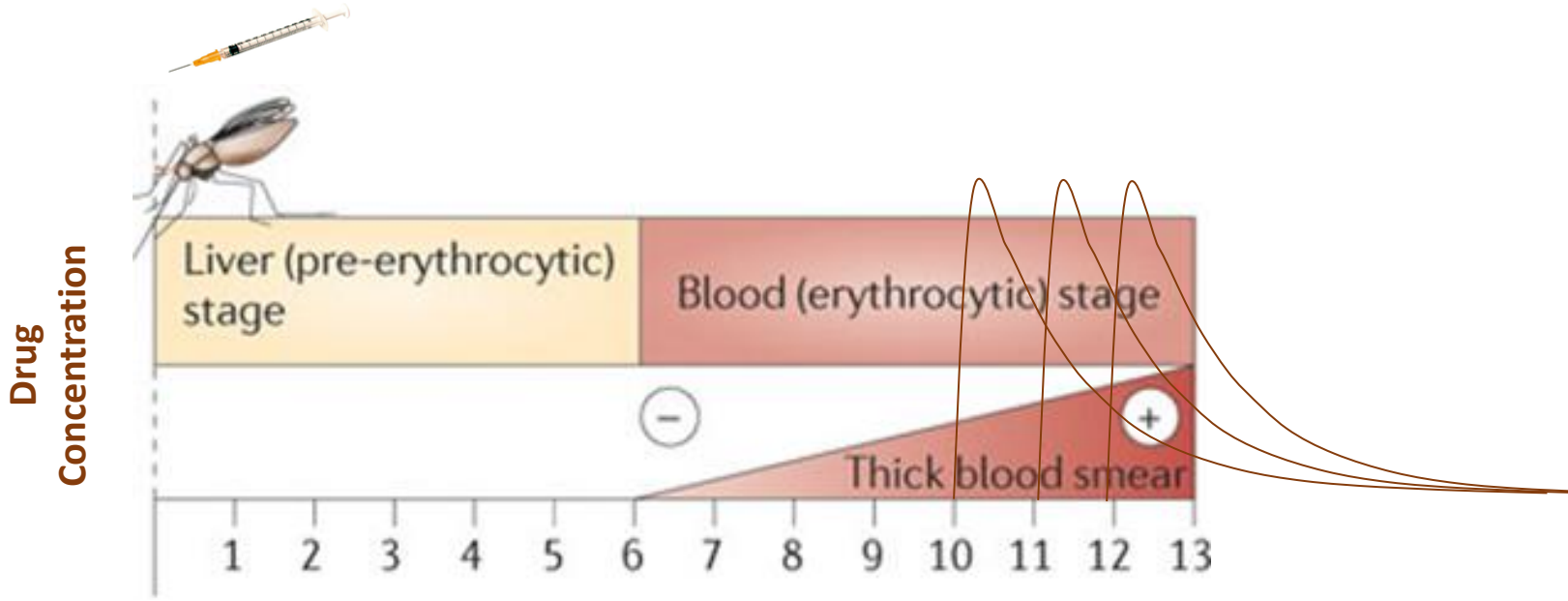
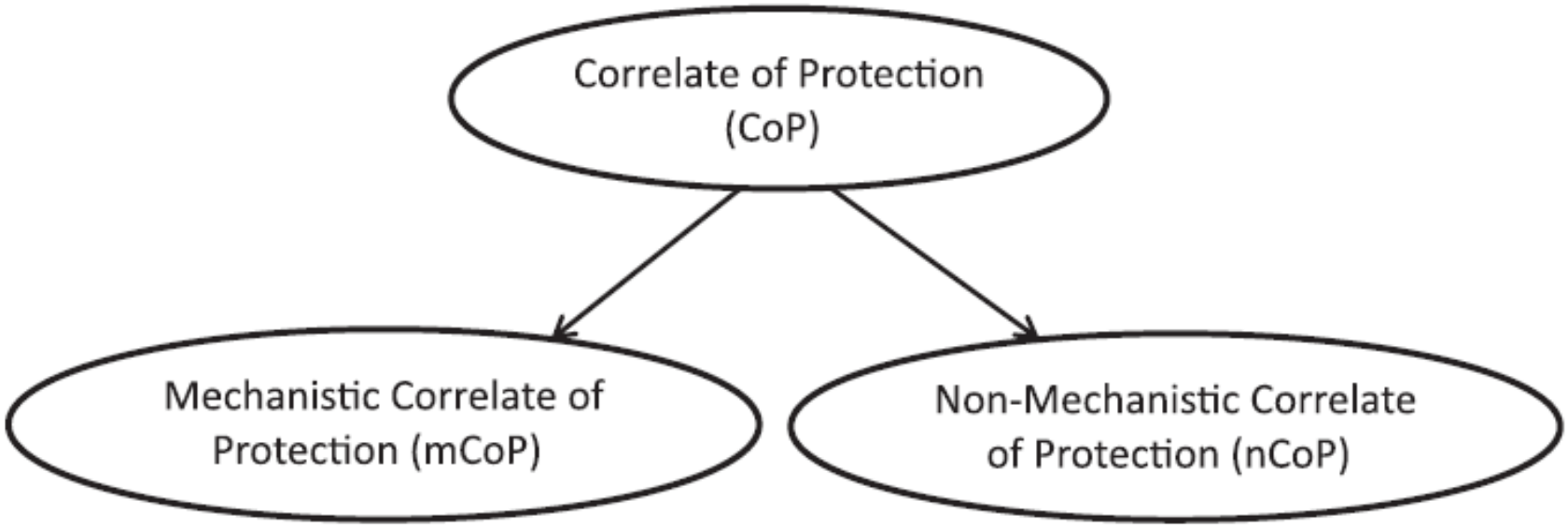
CHMI vis SIM (Dx with NAT)



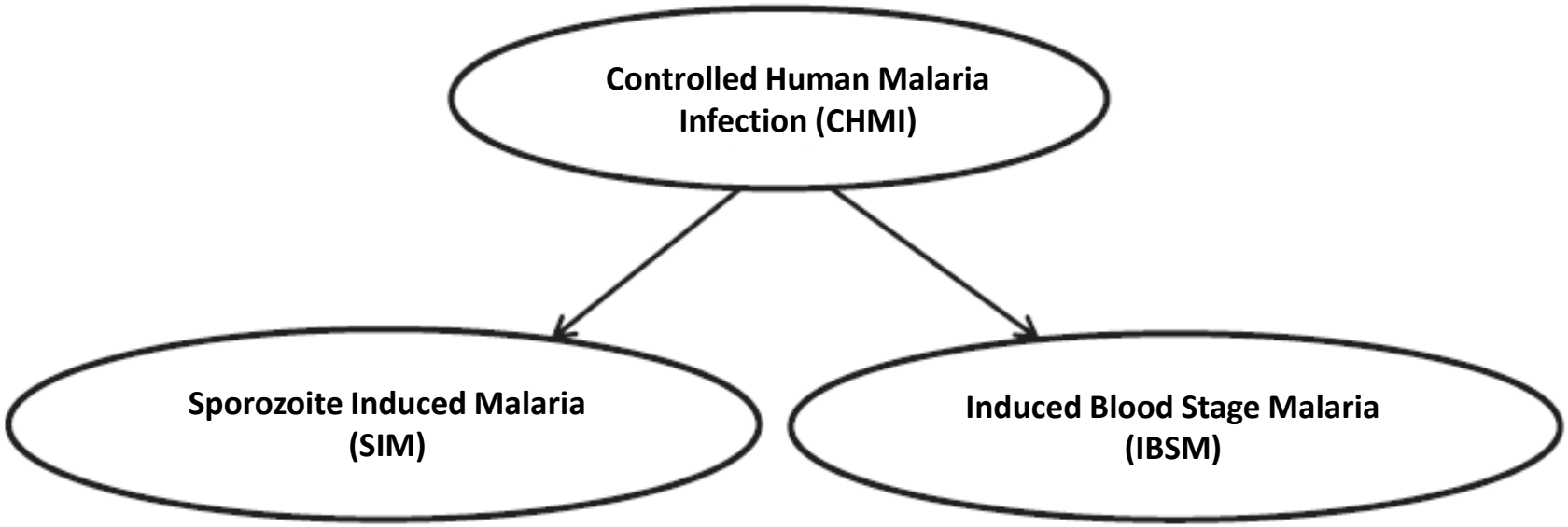
CHMI vis SIM (Dx with TBS)



Nested Nomenclature



Opportunities for Discovery



Acknowledgments

Study Participants

Fred Hutch: Kelly Shipman, Janine Maenza, David Berger, Sue Ferguson, Ryan Jensen, Laurie Rinn, Julie McElrath

Center for Infectious Disease Research: Stefan Kappe, Emma Fritzen, Tracie VonGoedert, Brandon Sack, Sebastian Mikolajczak

UW: Sean Murphy, Anna Wald, Wes Van Voorhis, Fred Buckner

MMV, DoD, BMGF, NIH

THANK YOU

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