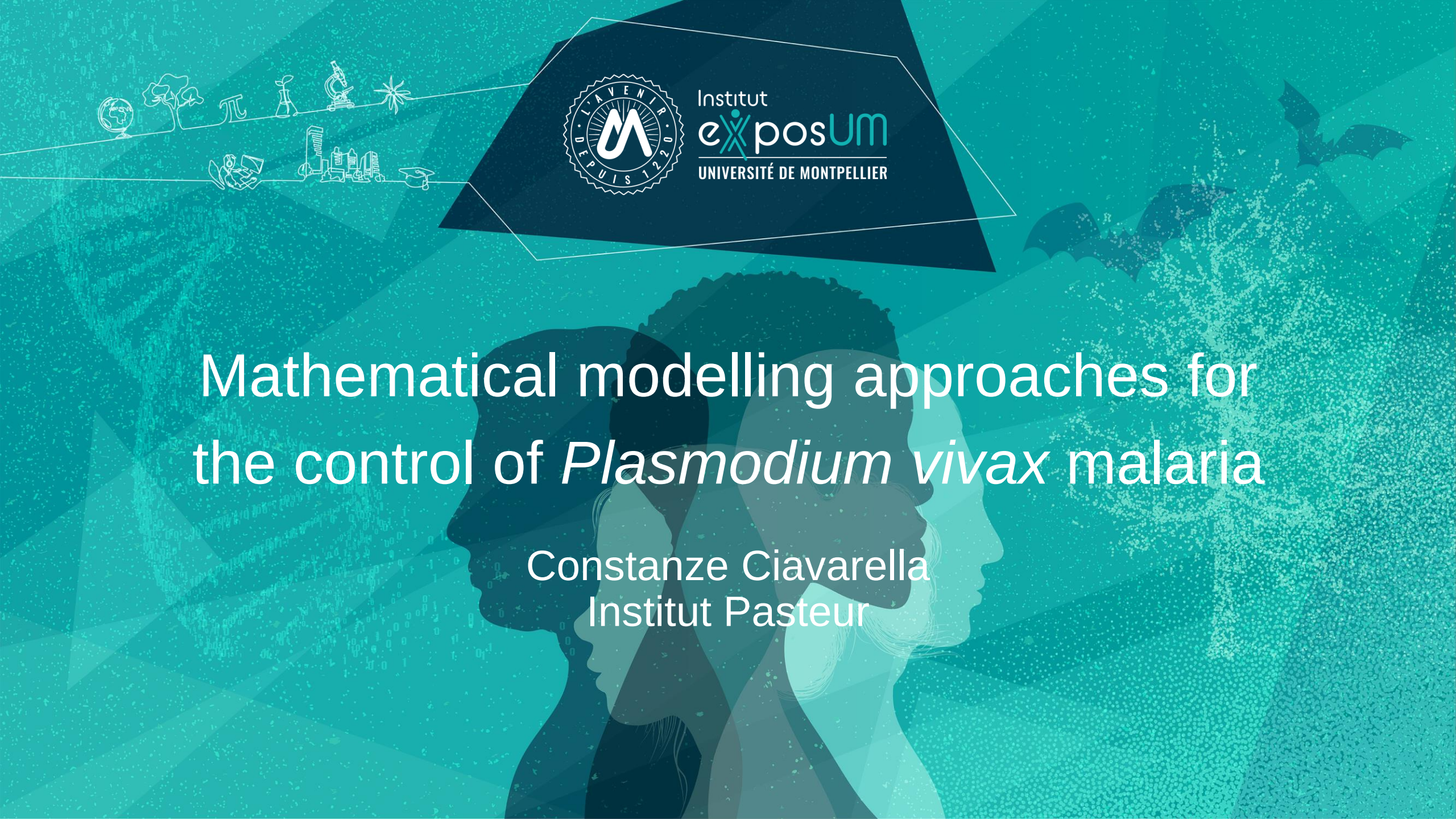


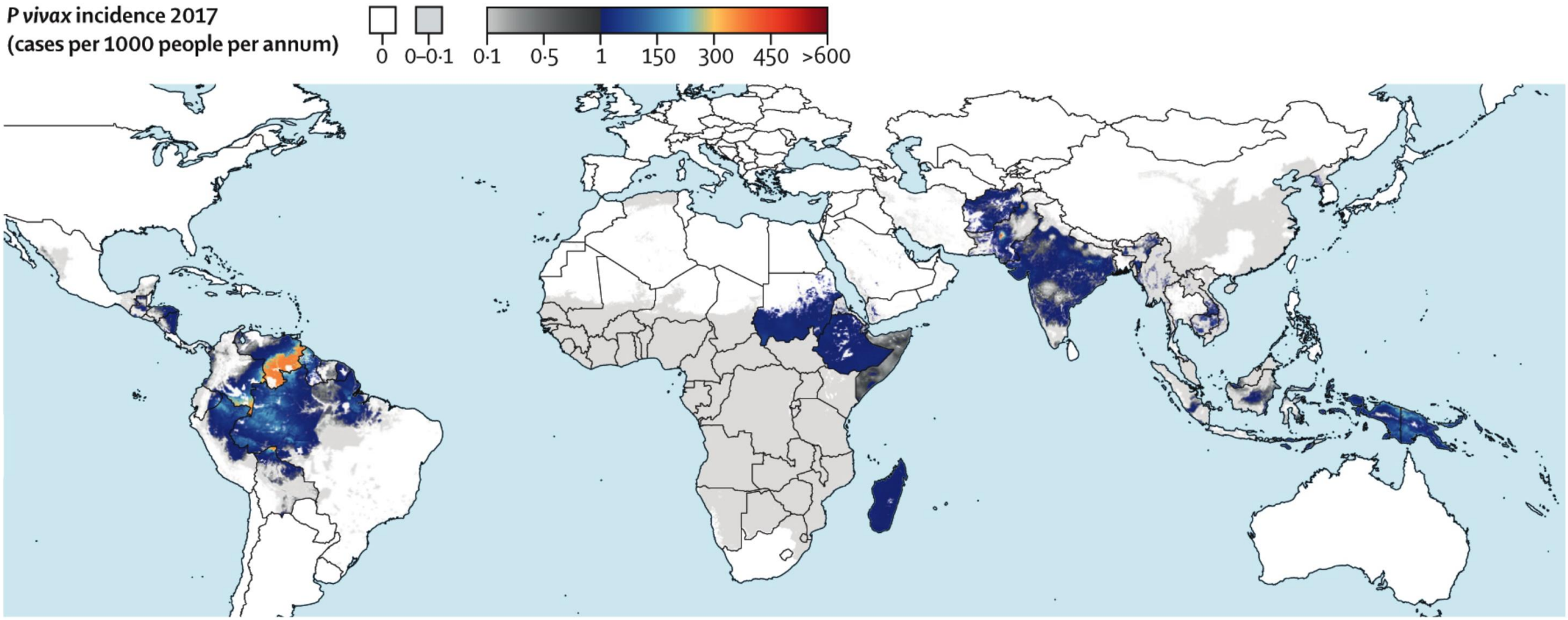
Mathematical modelling approaches for the control of *Plasmodium vivax* malaria

Constanze Ciavarella
Institut Pasteur

What is *P. vivax* malaria?

P. vivax – the “chronic” malaria

Geographical distribution of *P. vivax* malaria

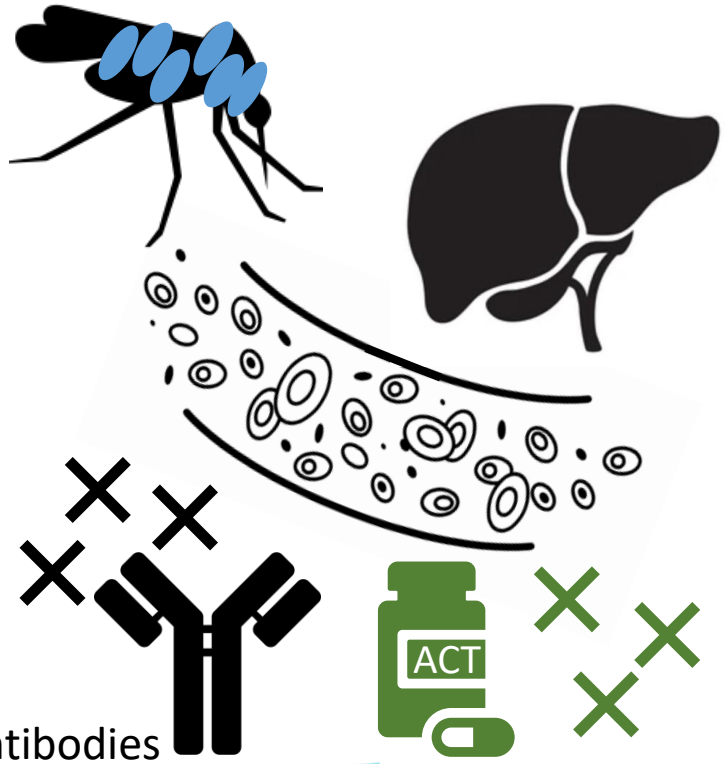


- *P. vivax:* 6.9 million clinical cases in 2022
- *P. falciparum*: 242 million clinical cases in 2022

Source: Battle *et al*, *The Lancet*, 2019

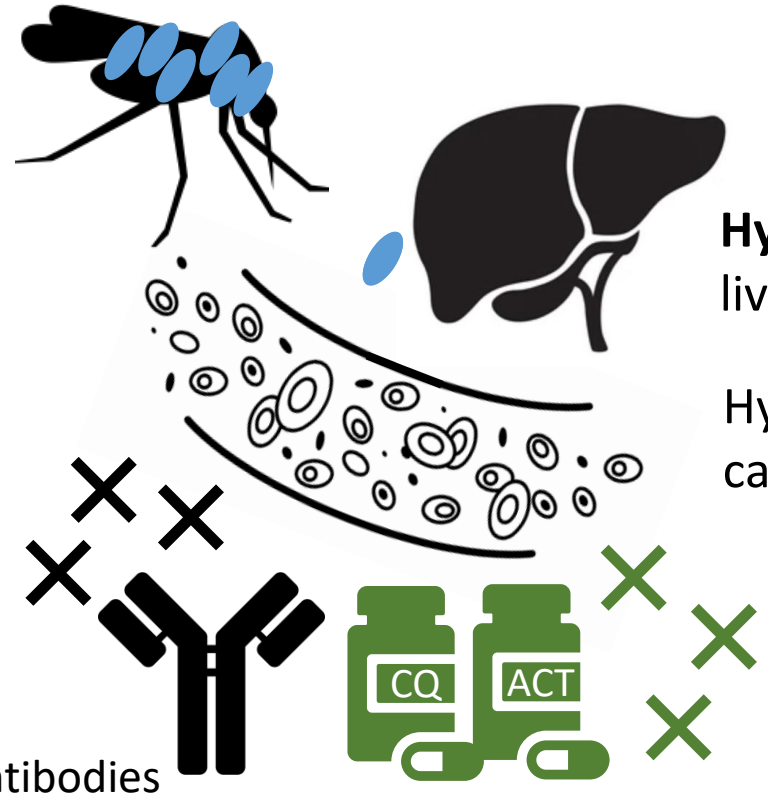
Malaria infection

P. falciparum infection



Artemisinin-based combination therapy (ACT)

P. vivax infection



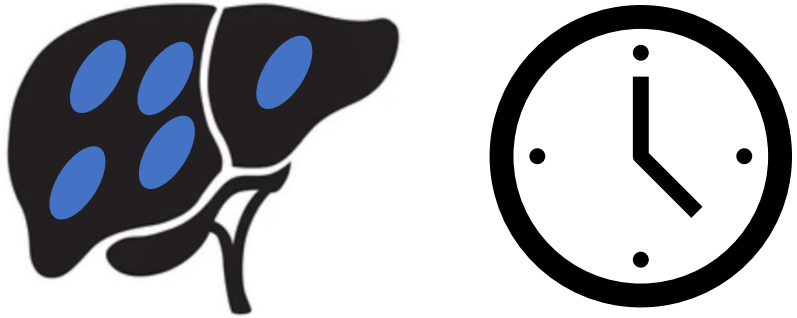
Hypnozoites: dormant liver stage parasites

Hypnozoite reactivation causes malaria **relapses**

Chloroquine (CQ) or ACT

Why is latent *P. vivax* hard to control?

1



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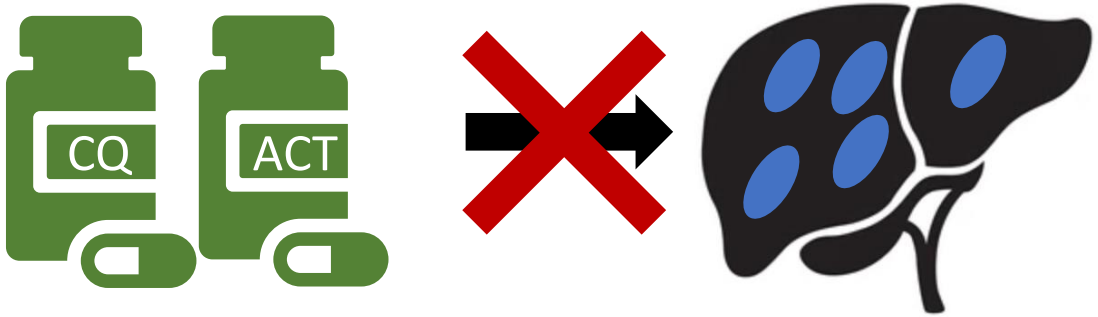

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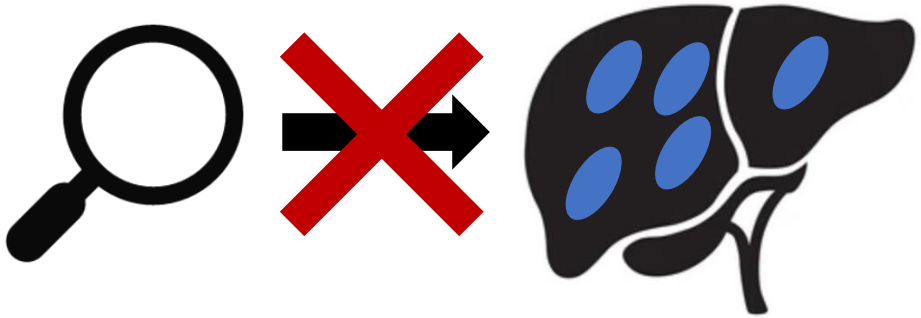

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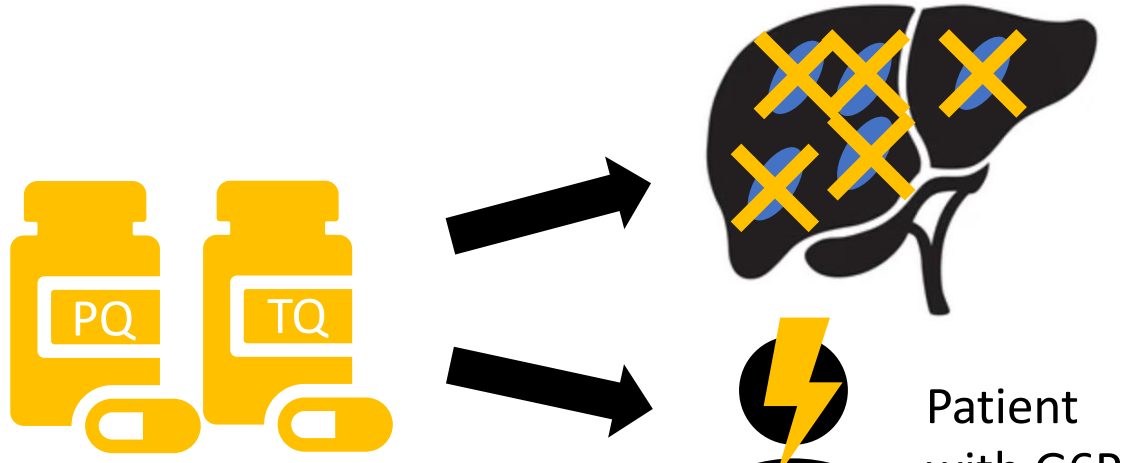
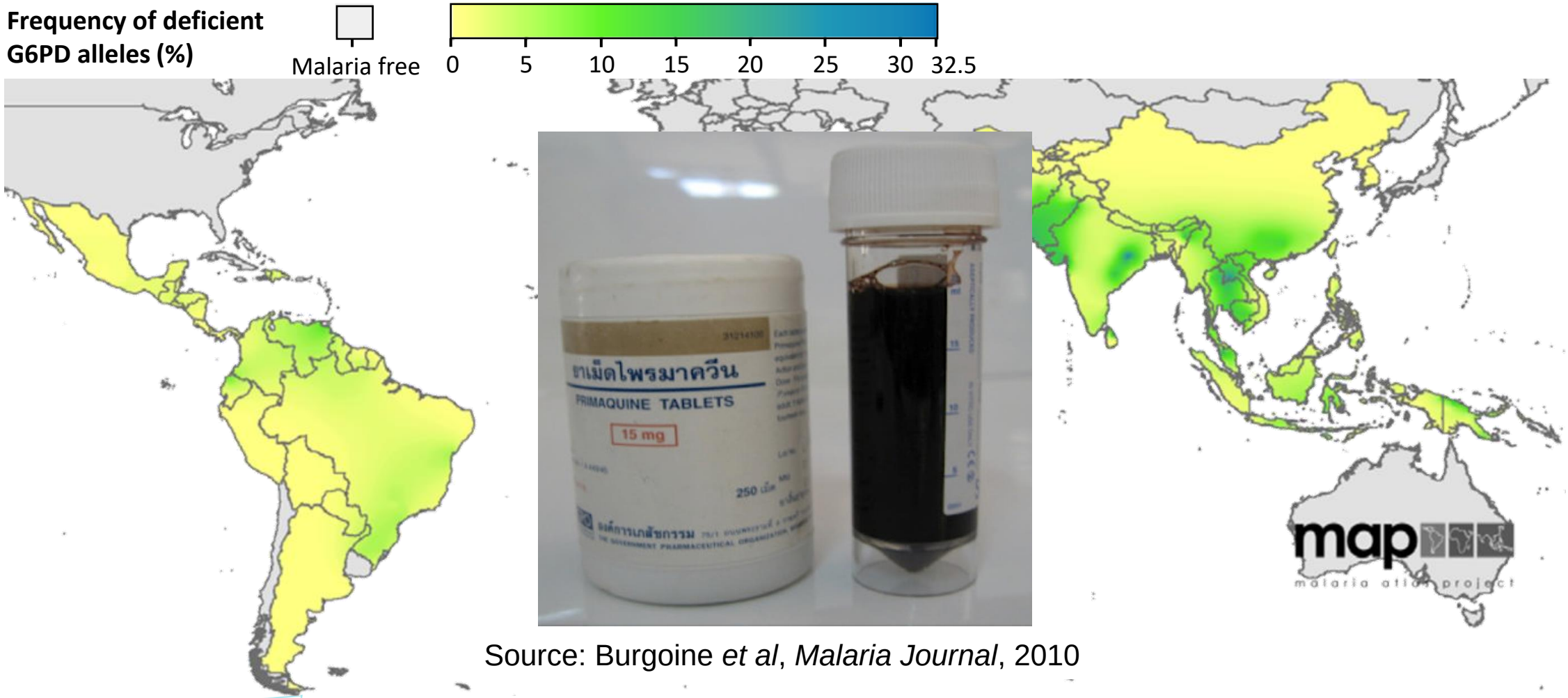


G6PD deficiency

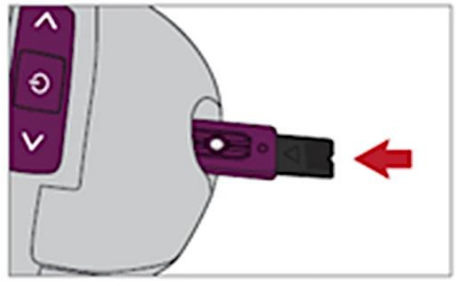


Source: Burgoine *et al*, *Malaria Journal*, 2010

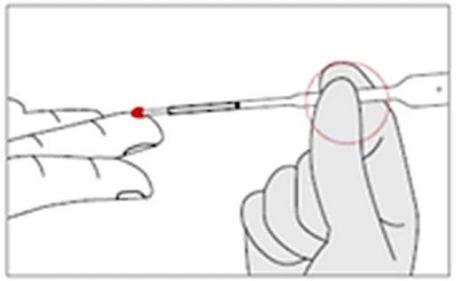
Source: Howes *et al*, *PLoS Medicine*, 2012

Testing for G6PD deficiency

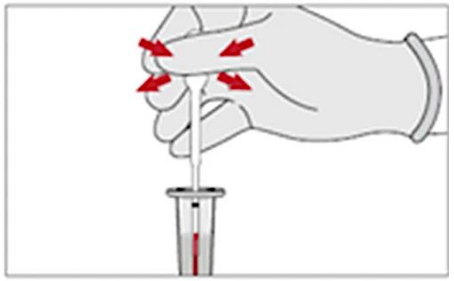
Test procedure for the SD Biosensor STANDARD G6PD Test



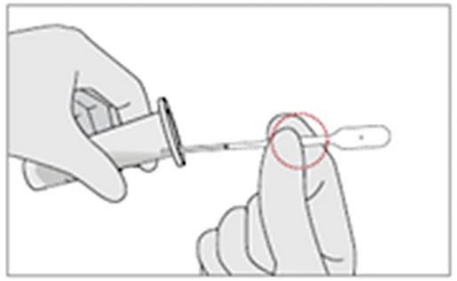
1. Insert test device into analyzer.



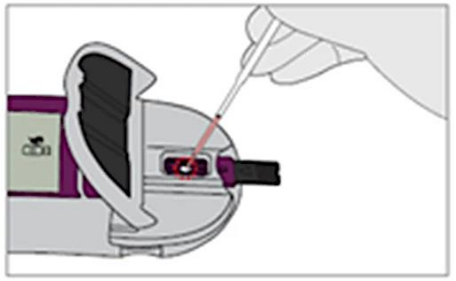
2. Collect blood.



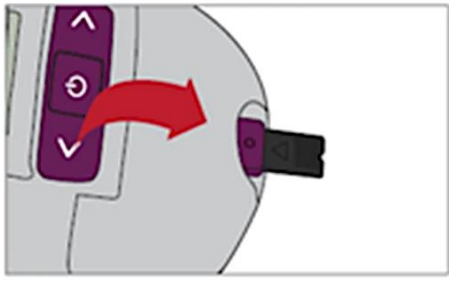
3. Mix blood and buffer 8–10 times.



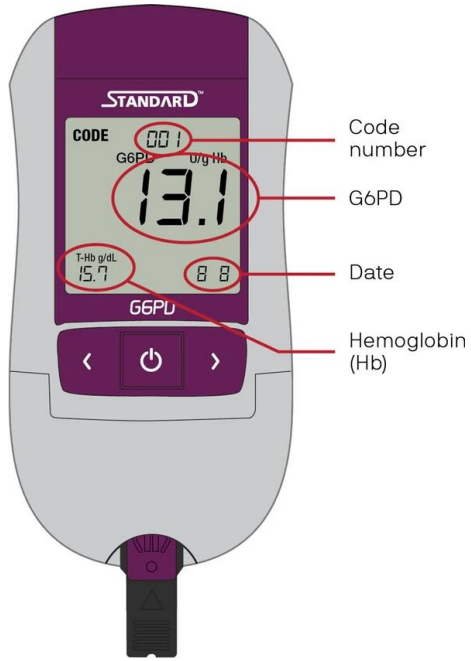
4. Collect mixed sample with NEW sample collector.



5. Apply the mixed sample to the hole in the test device.



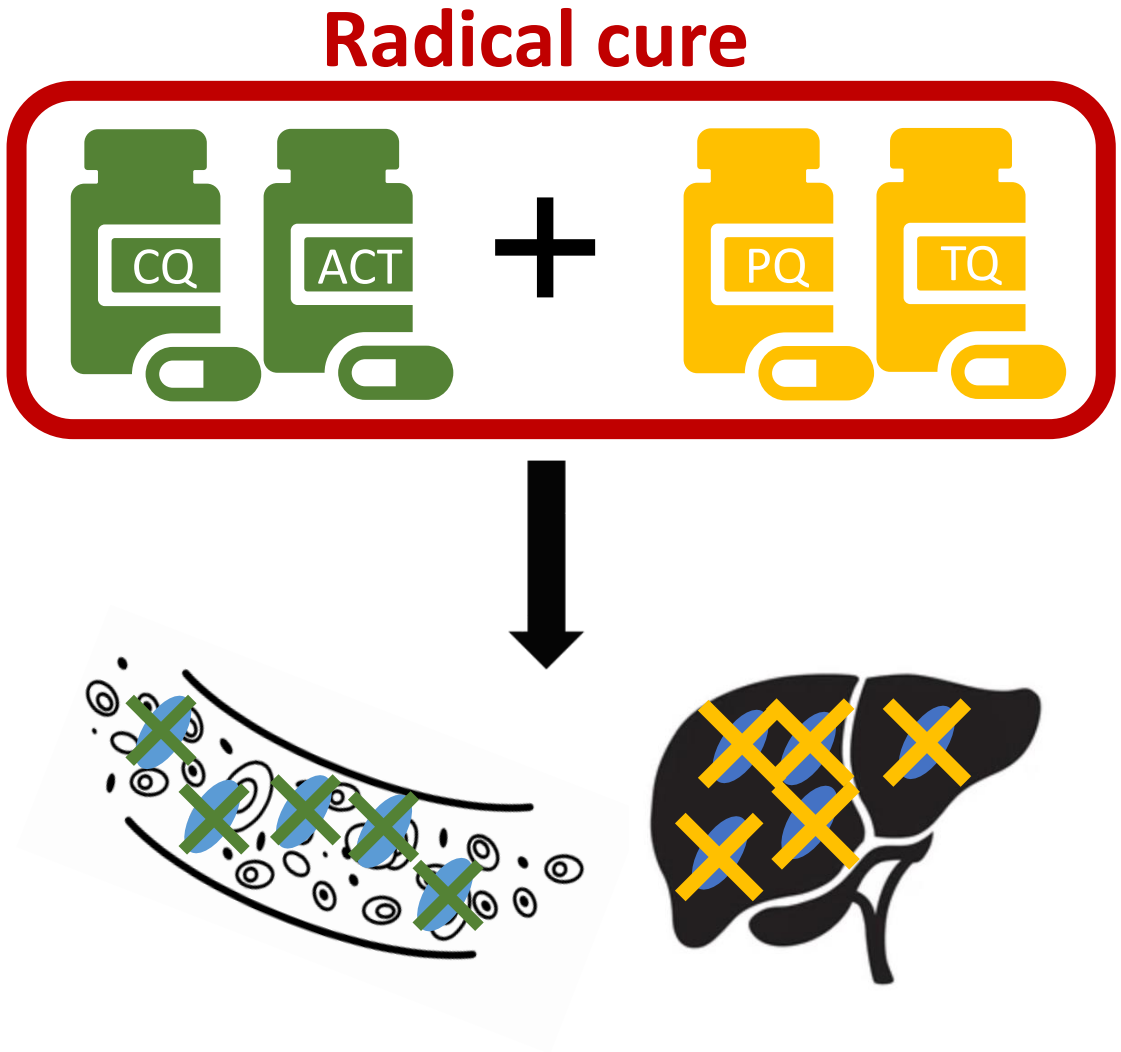
6. Close analyzer flap and wait for 2 minutes.



7. A quantitative measurement of G6PD activity and haemoglobin concentration will appear on the screen.

Source: Gerth-Guyette *et al*, *Malaria Journal*, 2021

Radical cure: a new tool against *P. vivax*

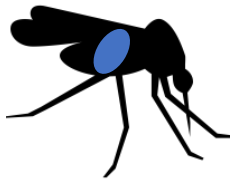


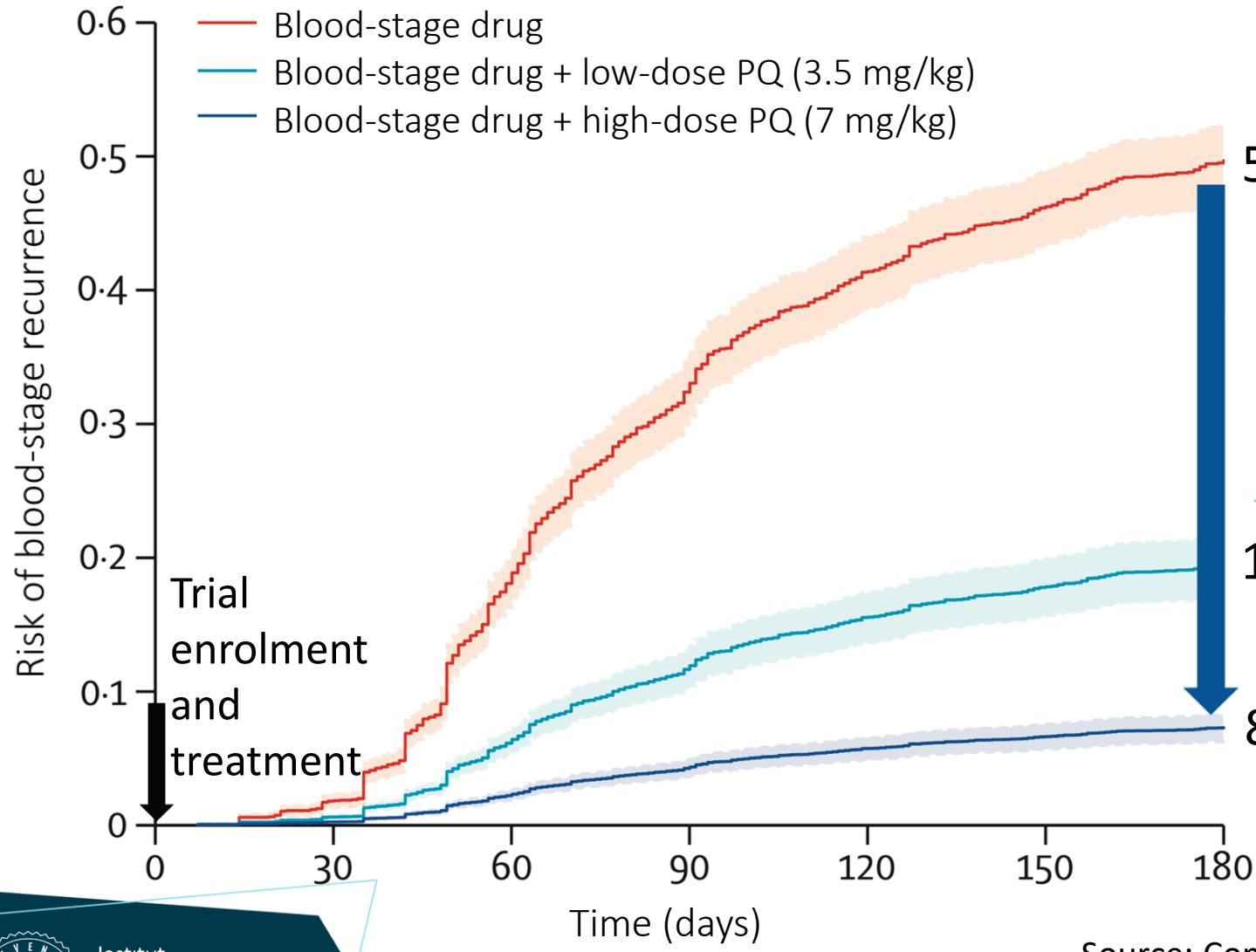
What is the hypnozoiticidal efficacy of PQ and TQ?

A modelling approach to estimate PQ and TQ efficacy from clinical trial data

Clinical trial data

Recurrence = reinfection + relapse





51.0%

Risk of blood-stage recurrence reduced by 62.2%

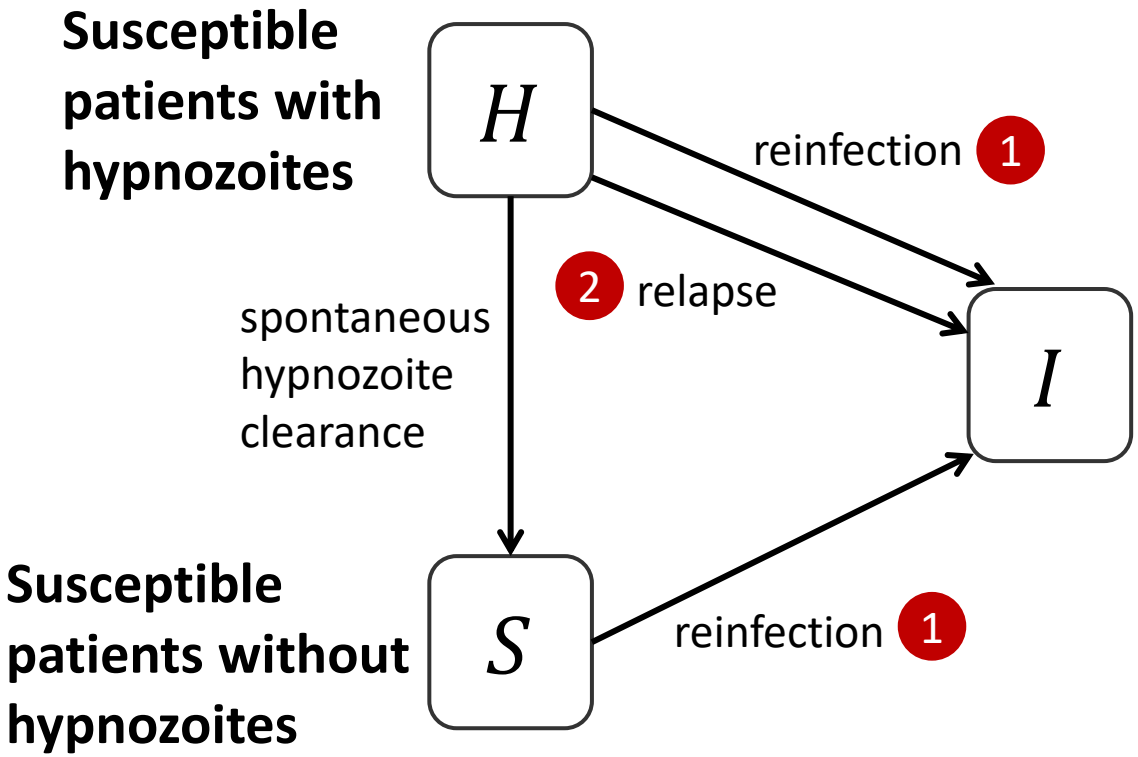
19.3%

Risk of blood-stage recurrence reduced by 84.1%

8.1%

Source: Commons et al, *The Lancet Infectious Diseases*, 2023

Modelling blood-stage recurrence in a clinical trial arm



$$\begin{cases} H(0) = 1 - efficacy \ \textcircled{3} \\ S(0) = efficacy \ \textcircled{3} \\ I(0) = 0 \end{cases}$$

Estimated parameters

1 2 for each trial location

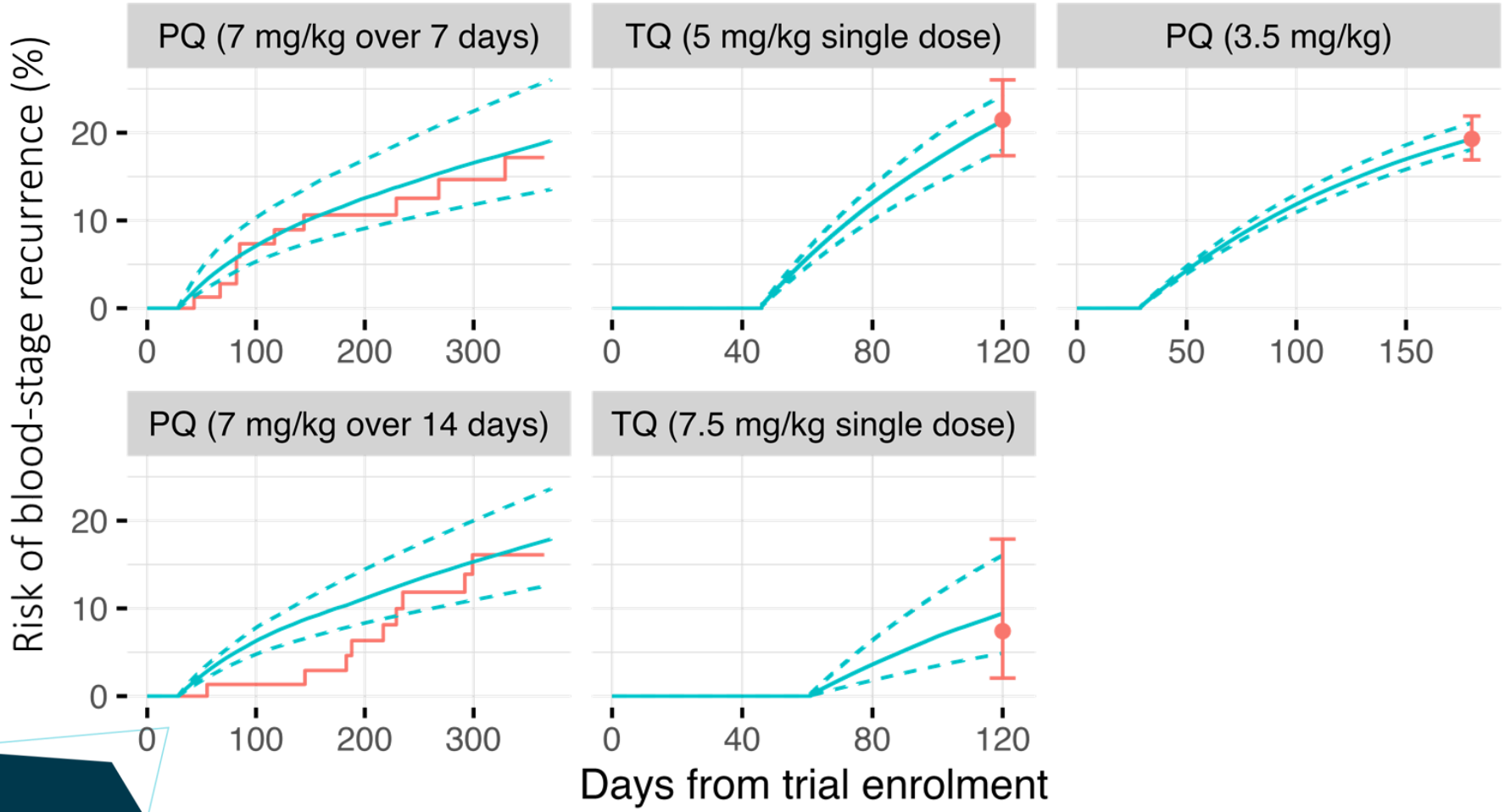
3 for each drug regimen

Fitting the model to data from various clinical trials

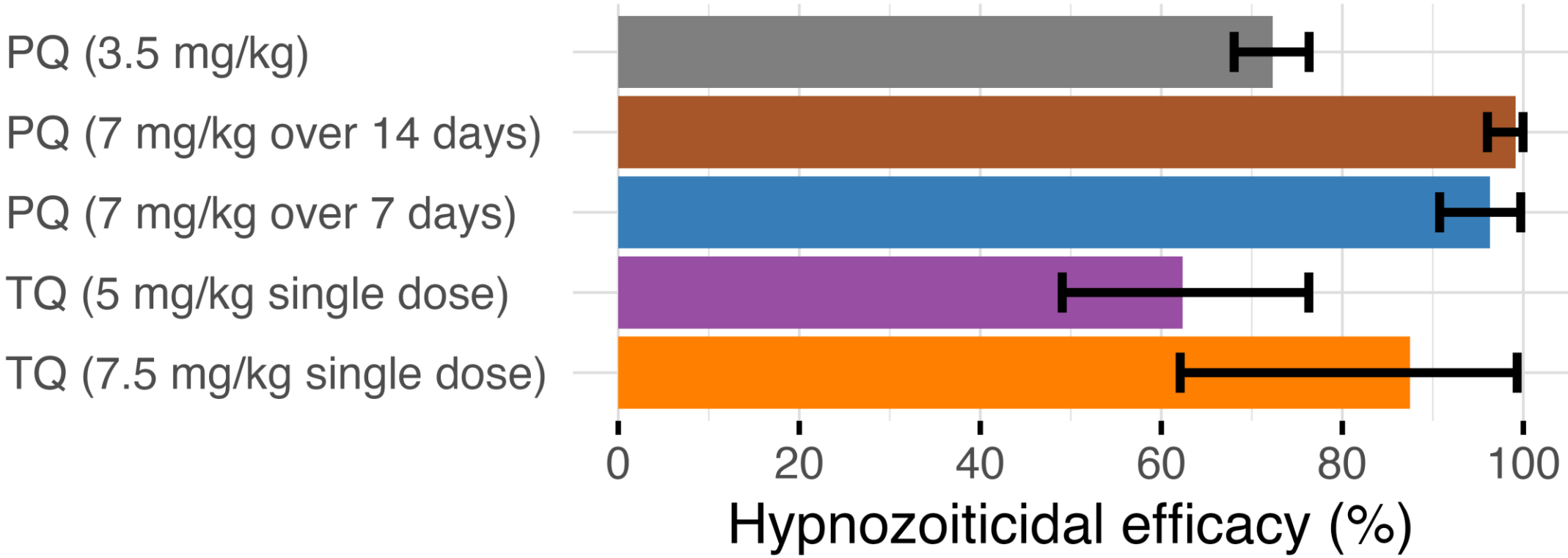
Patient-level clinical data
Taylor et al, *Lancet*, 2019

Aggregated clinical data
Watson et al, *eLife*, 2022

Aggregated clinical data
Commons et al, *Lancet Infect Dis*, 2023



Hypnozoiticidal efficacy estimates



Patient-level perspective: trial vs. operational conditions

Accounting for patients' eligibility criteria and imperfect treatment adherence

Trial-like and real-world conditions

Conditions	Cohort	Drug eligibility	Drug adherence
Trial conditions	Clinical cases that have been enrolled in a trial	Trials only enrol eligible patients	100% (assuming directly observed treatment)
Operational conditions	Clinical cases	Restrictions based on • G6PD activity level • Age • Pregnancy and breastfeeding status	• TQ single dose – 100% • PQ over 7 days – 67% • PQ over 14 days – 57%

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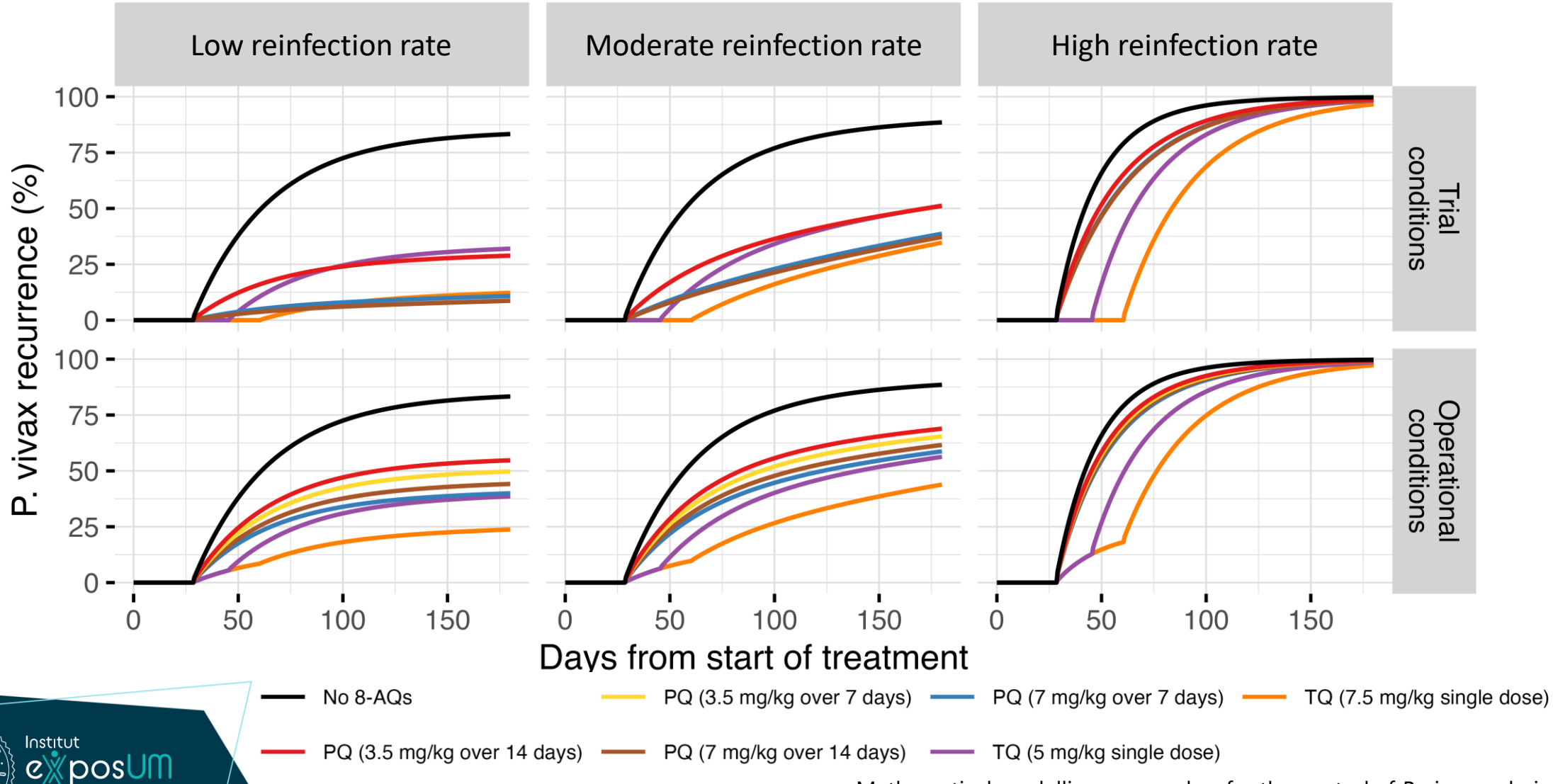
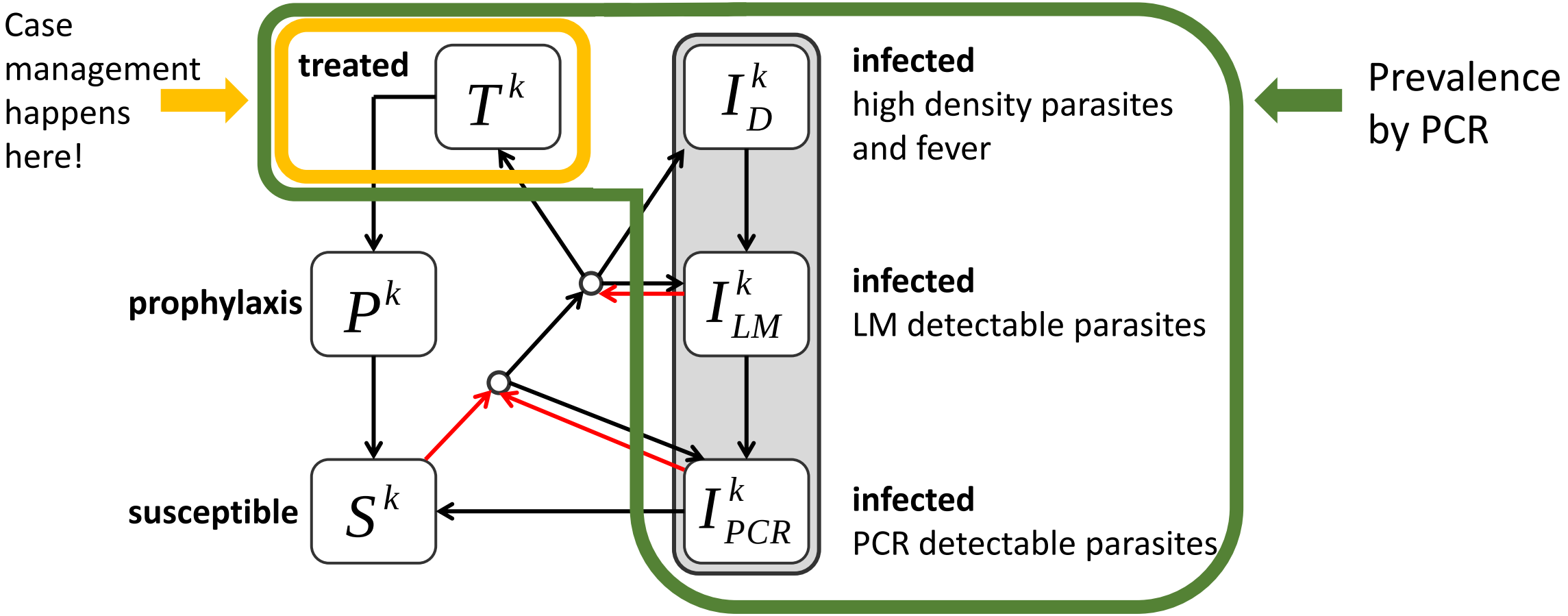
Per-person probability of blood-stage recurrence in follow-up



How does radical cure case management impact *P. vivax* transmission?

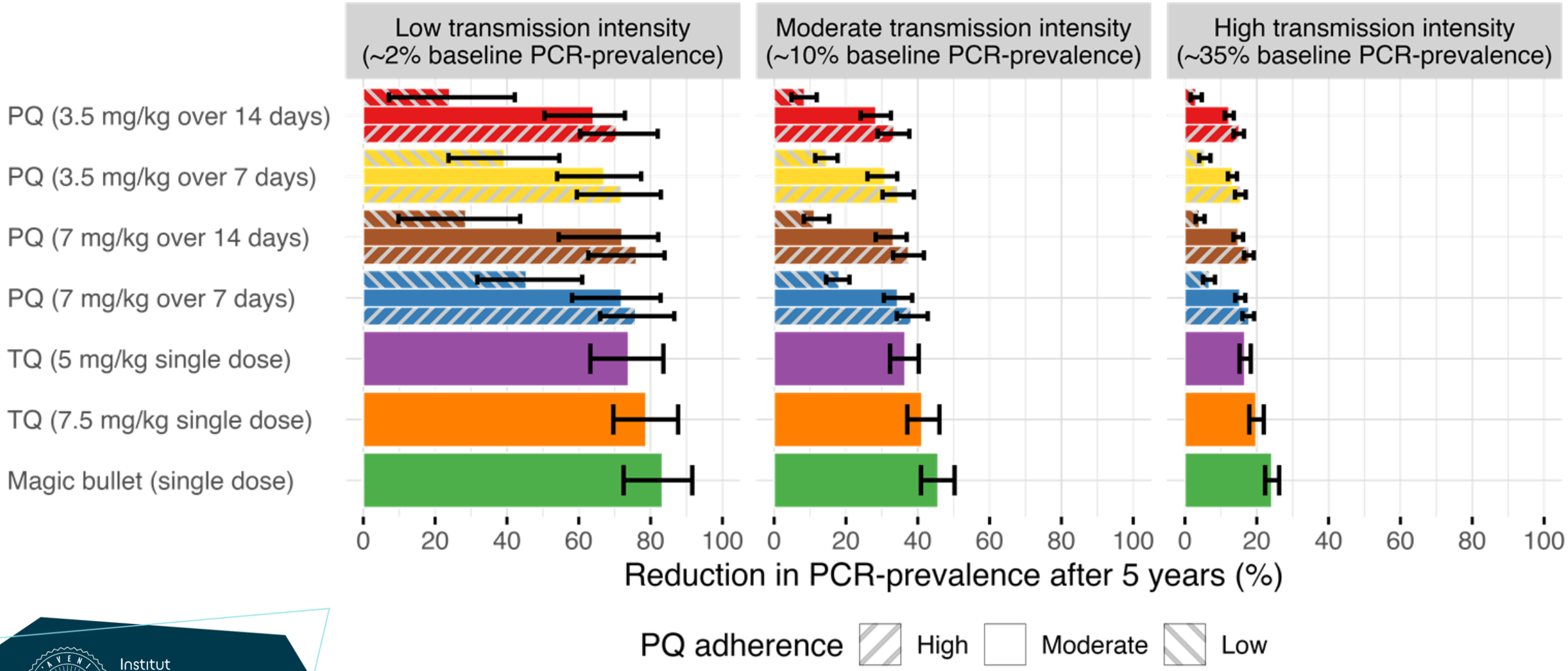
An individual-based model to simulate treating symptomatic patients with radical cure

Individual-based model of *P. vivax* transmission



Source: White *et al*, *Nature Communications*, 2018

Population reduction in estimated PCR-prevalence after 5 years of radical cure case management

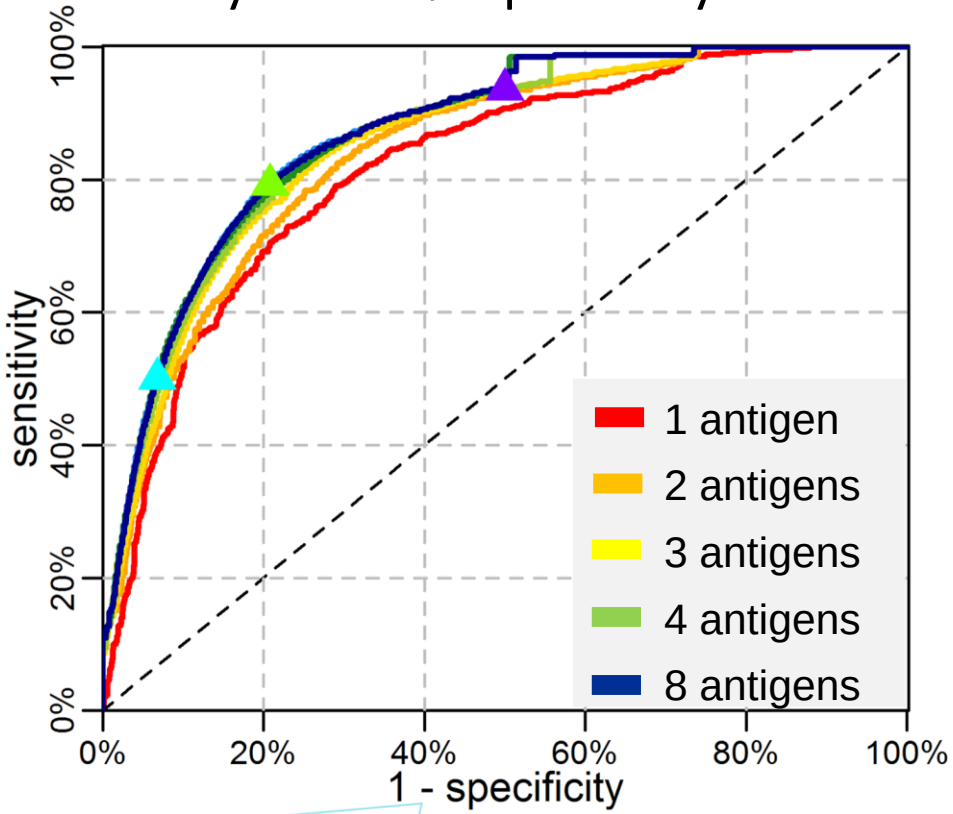


How can we detect and target *P. vivax* malaria?

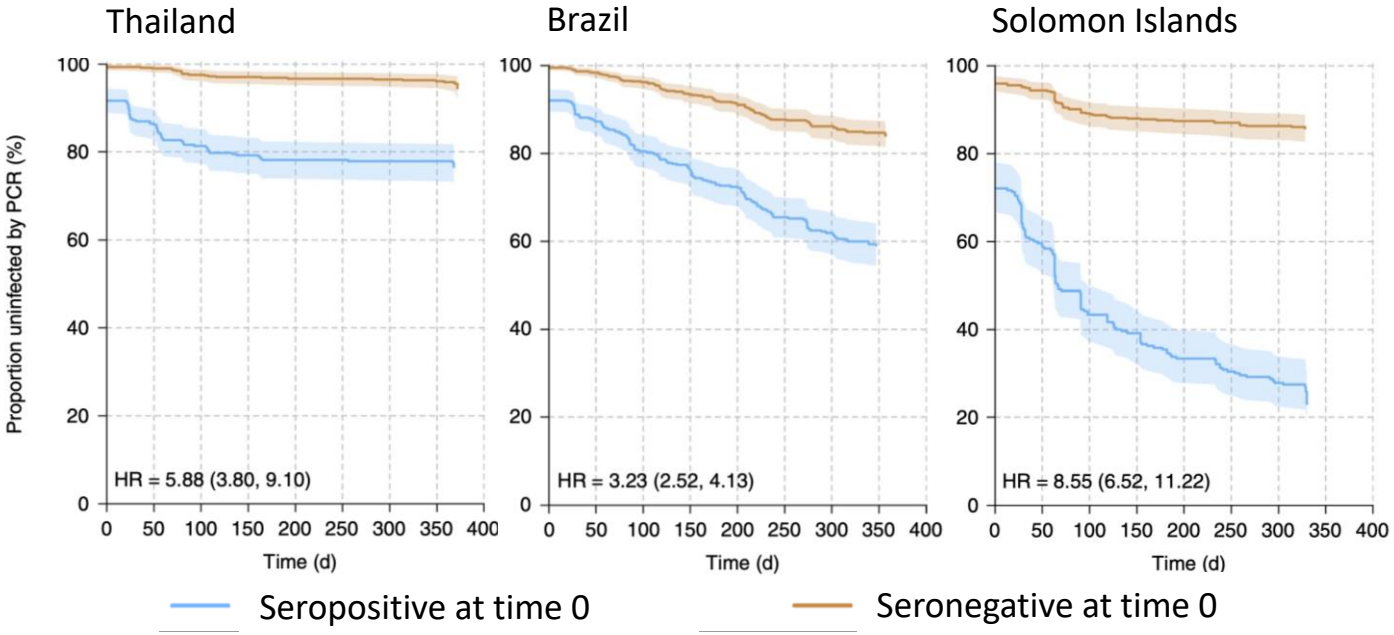
An active case detection strategy based on previous results in the team

Serological diagnostics for *P. vivax*

Serological test is able to detect recent (<9m) blood-stage infections with 80% sensitivity and 80% specificity



Seropositives have been shown to recur faster -> more likely to carry hypnozoites



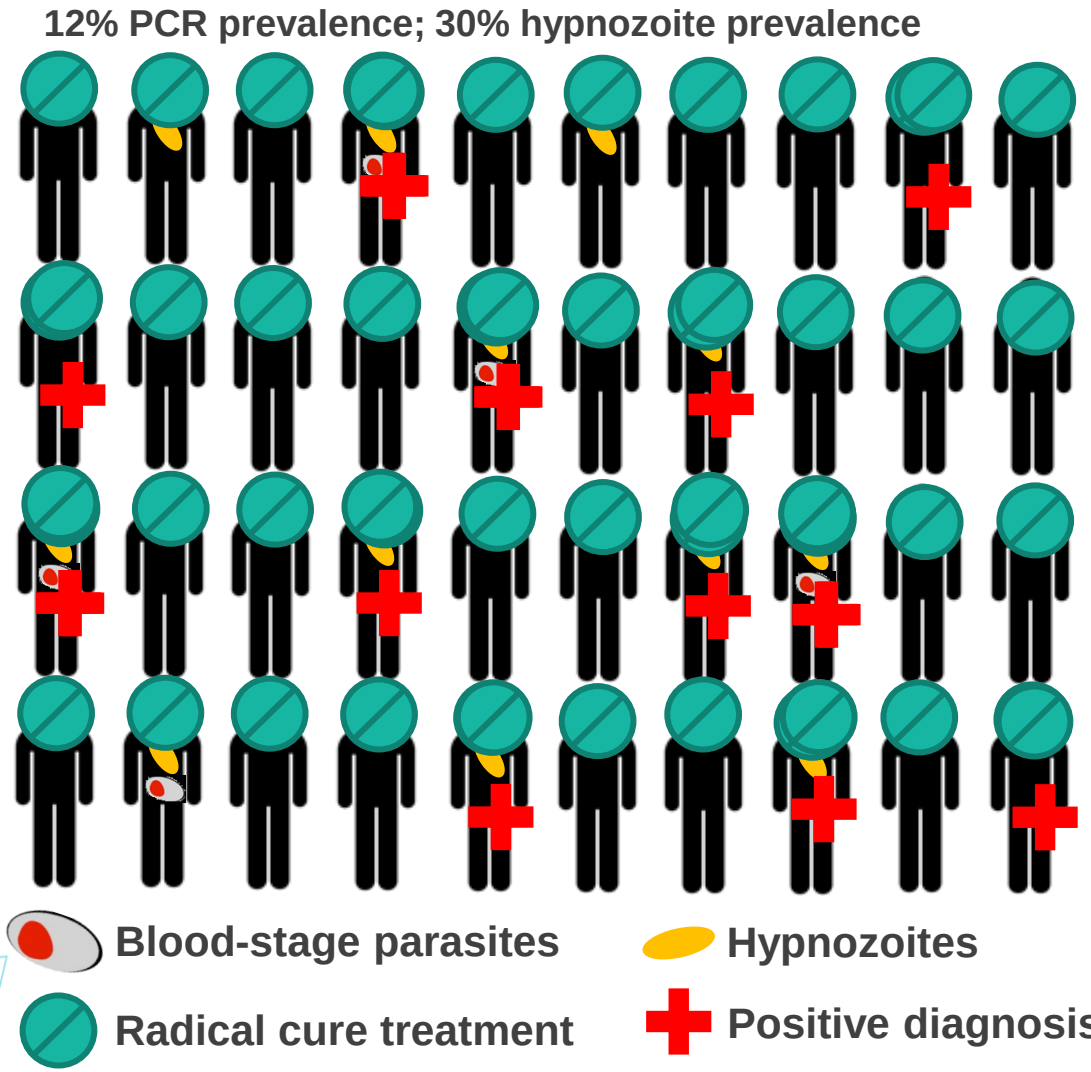
Source: Longley, White *et al*, *Nature Medicine*, 2020

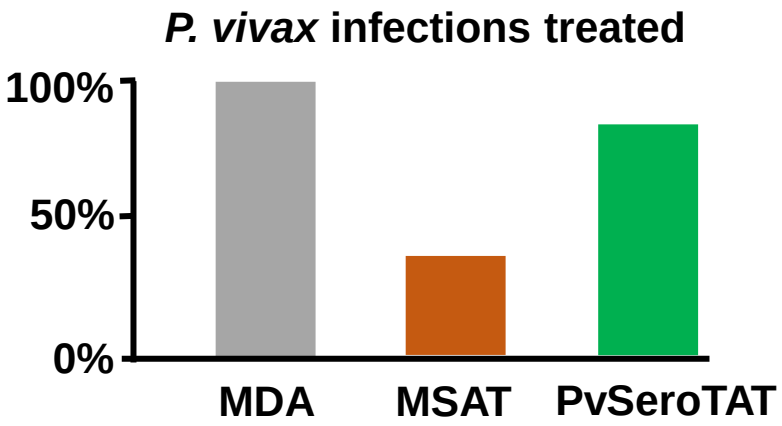
Active case detection strategies for *P. vivax*

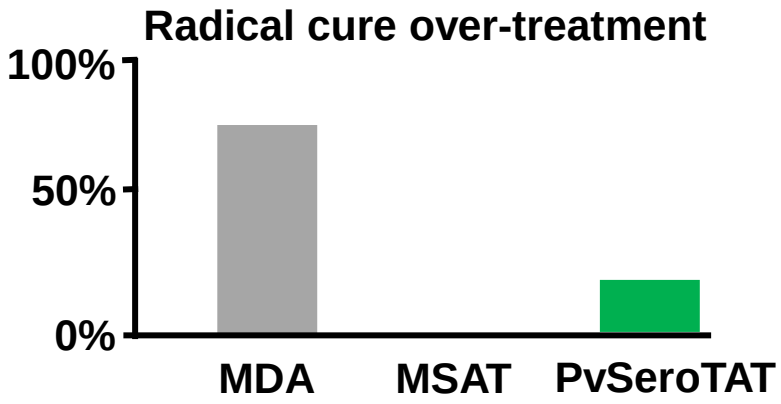
Mass Drug Administration (MDA)
- 100% coverage

Mass Screen and Treat (MSAT)
- 80% sensitivity

Serological Testing and Treatment (PvSeroTAT)
- 80% sensitivity & 80% specificity







Source: Obadia *et al*, *BMC Medicine*, 2022

PvSTATEM: *P. vivax* Serological Testing and Treatment in Ethiopia and Madagascar

PvSTATEM

Co-funded by the European Union

INSTITUT PASTEUR

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Ahri
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FIND
Diagnosis for all

MEDEA

WEHI
brighter together

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Warsaw University of Technology

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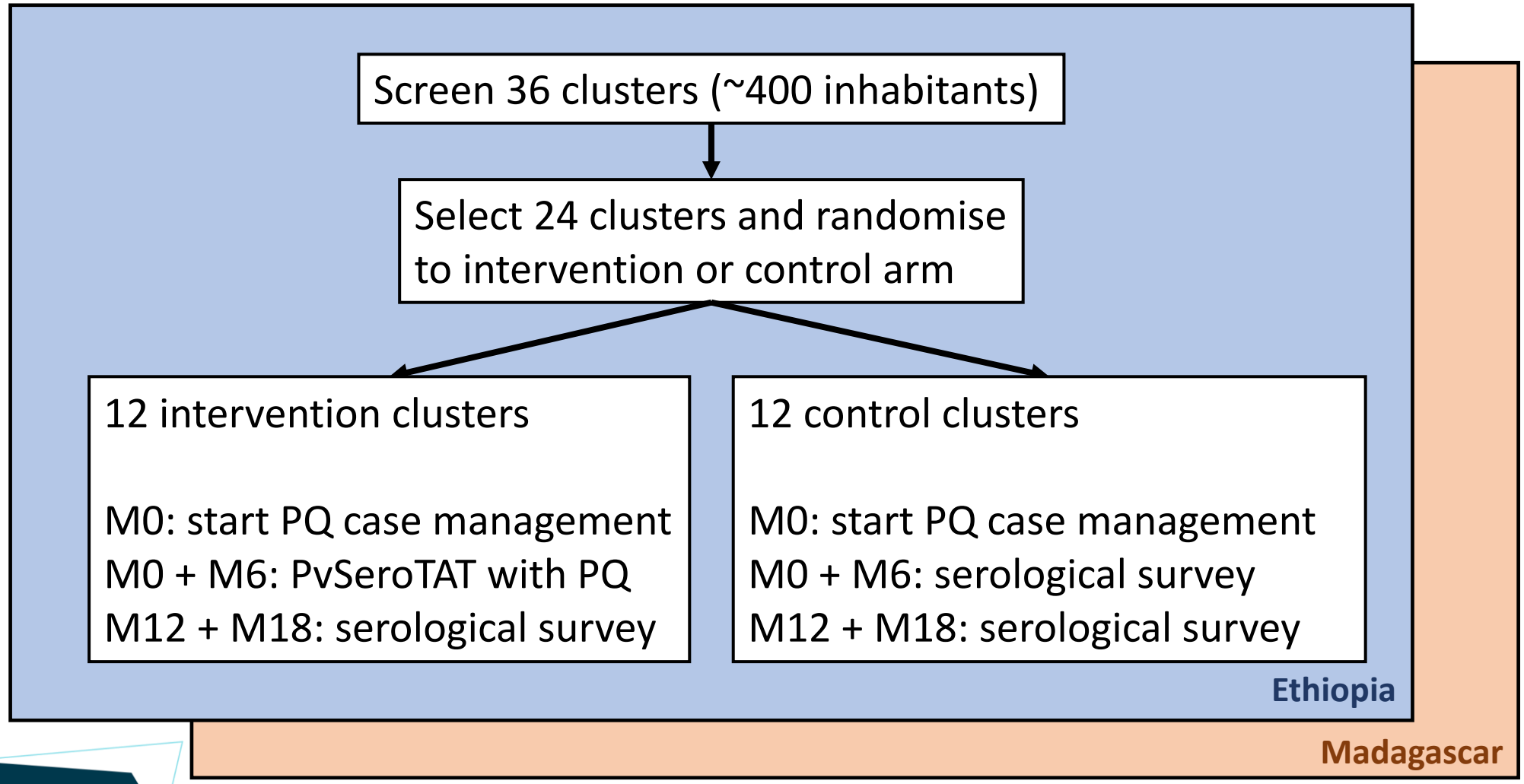
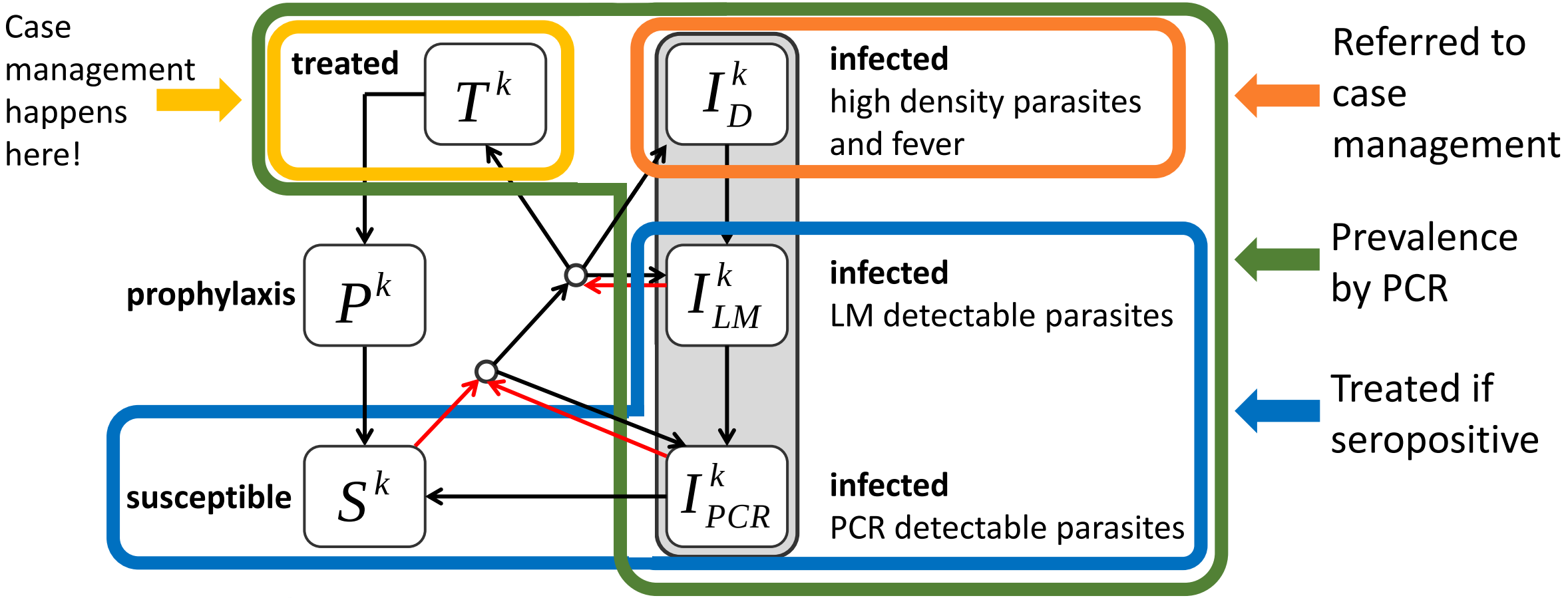
PvSTATEM design summary



How can modelling guide trial design and roll-out?

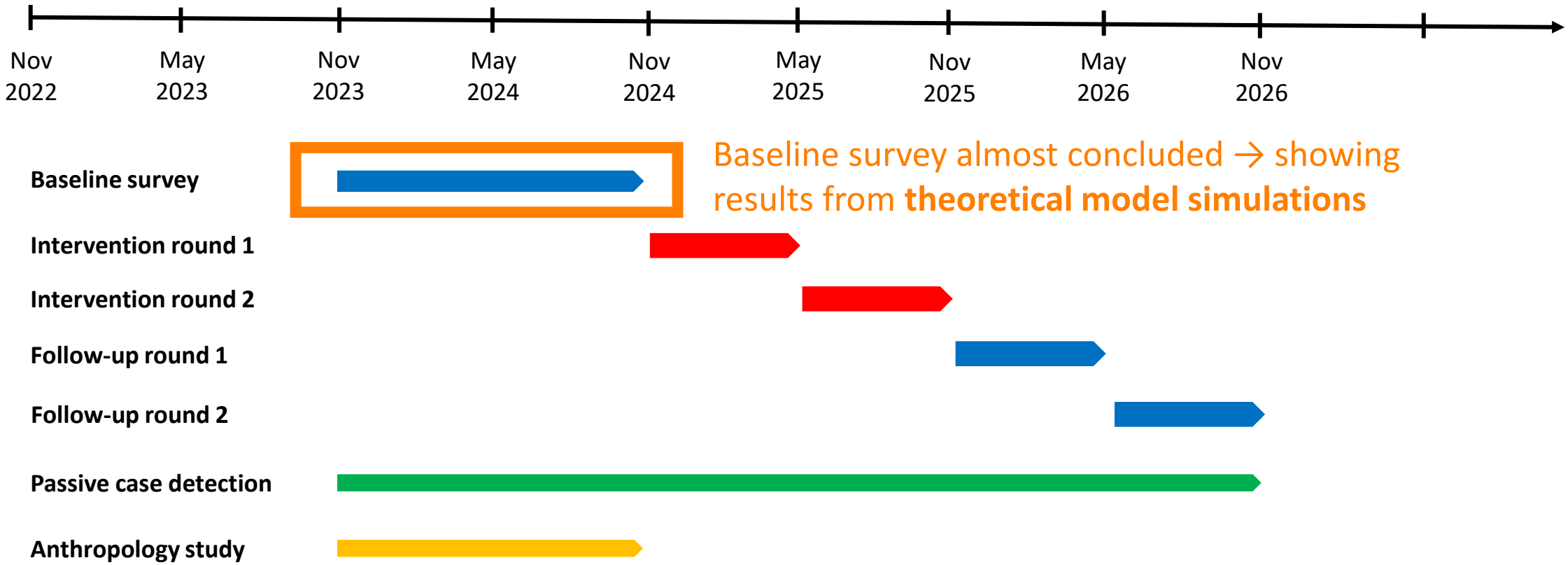
Simulating the PvSTATEM cluster-randomised clinical trial

Individual-based model of *P. vivax* transmission



Source: White *et al*, *Nature Communications*, 2018

PvSTATEM timeline



Trial simulations

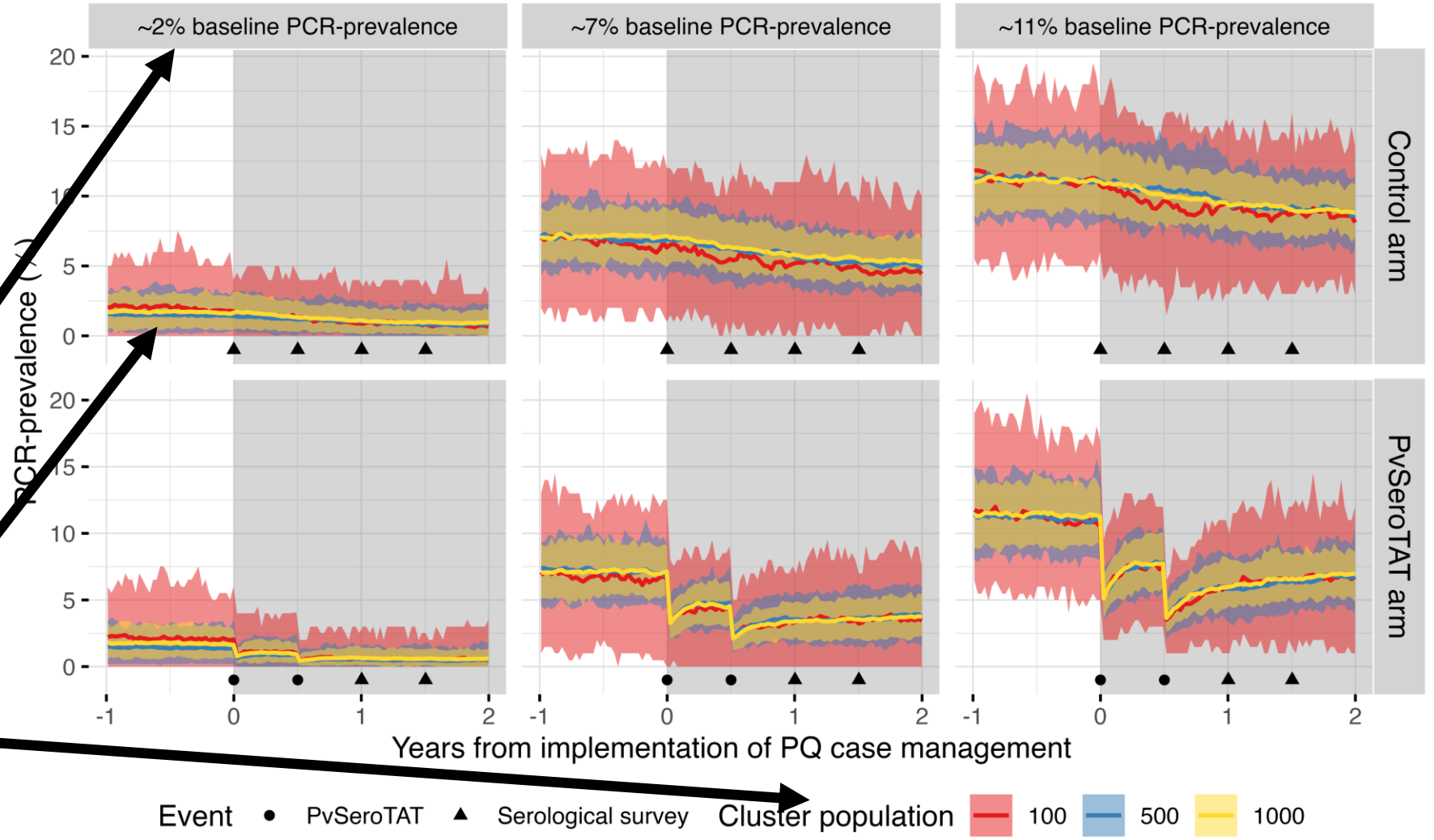
"Theoretical" simulations

Simulate the trial protocol in a range of verisimilar transmission settings

PvSTATEM simulations

Incorporate data from PvSTATEM baseline survey:

- Pre-intervention PCR-prevalence
- Transmission seasonality
- Cluster population



Inform choice of PQ regimen for intervention arm

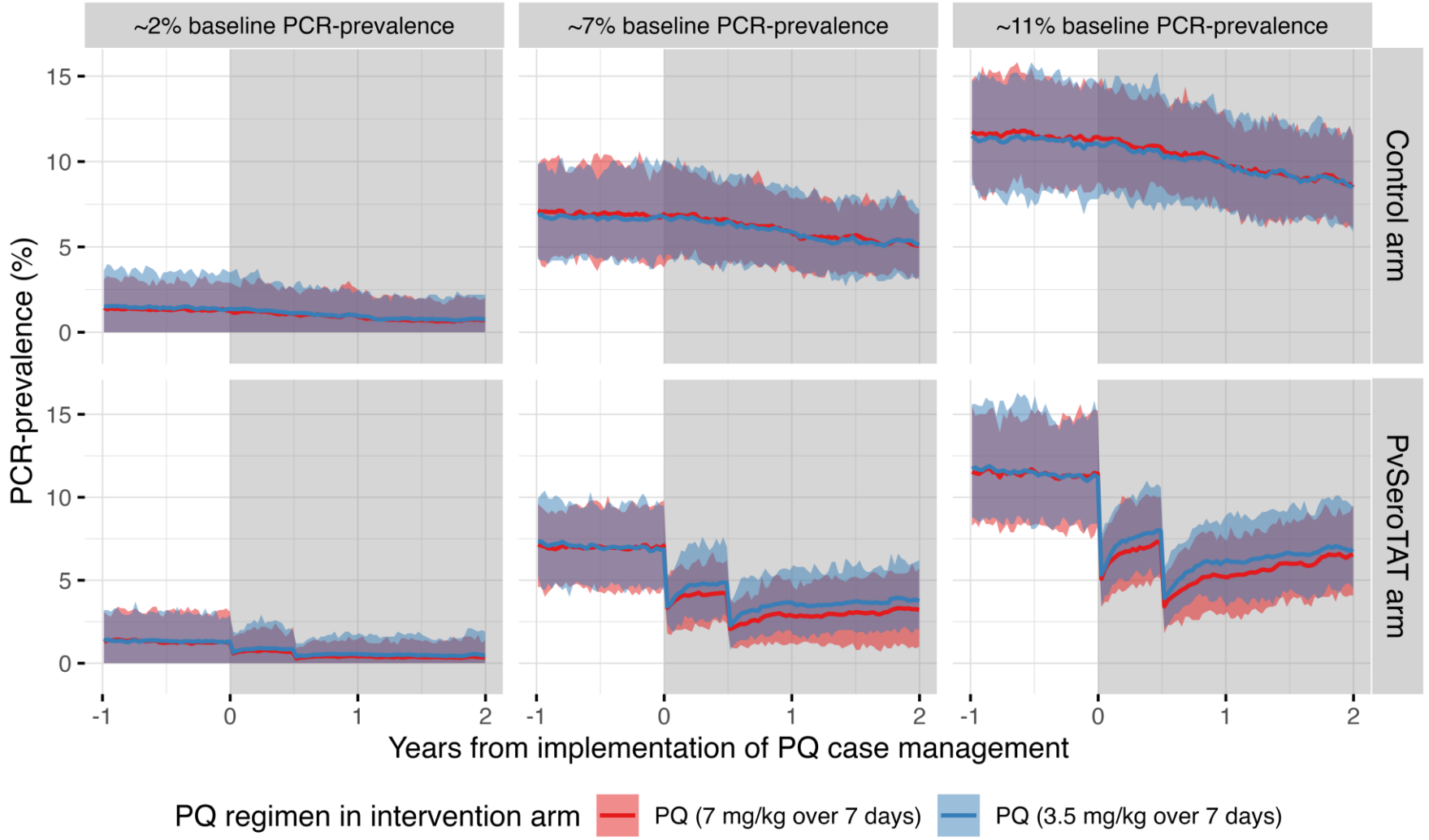
Question

What PQ dosage to prescribe?

- 3.5 mg/kg (= national guidelines)
- 7 mg/kg

Status

Done (June 2023)



Inform choice of clusters to retain in trial

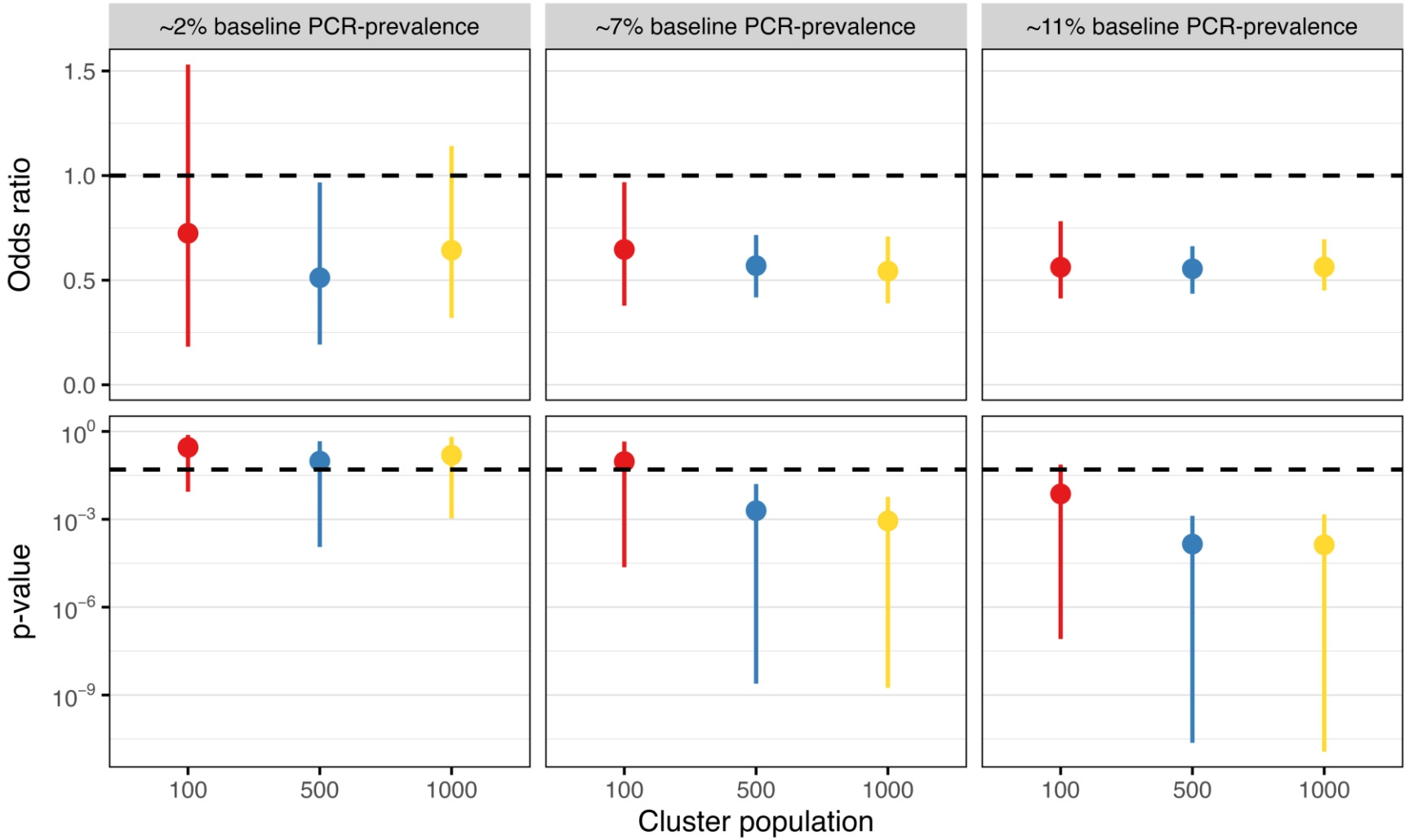
Question
Which of the 36 screened clusters should be retained?

Primary endpoint
PCR-prevalence at 6 months after second round of PvSeroTAT

Status
Theoretical simulations

Next steps
Incorporate baseline survey data

Output
Cluster features that maximise likelihood of successful trial



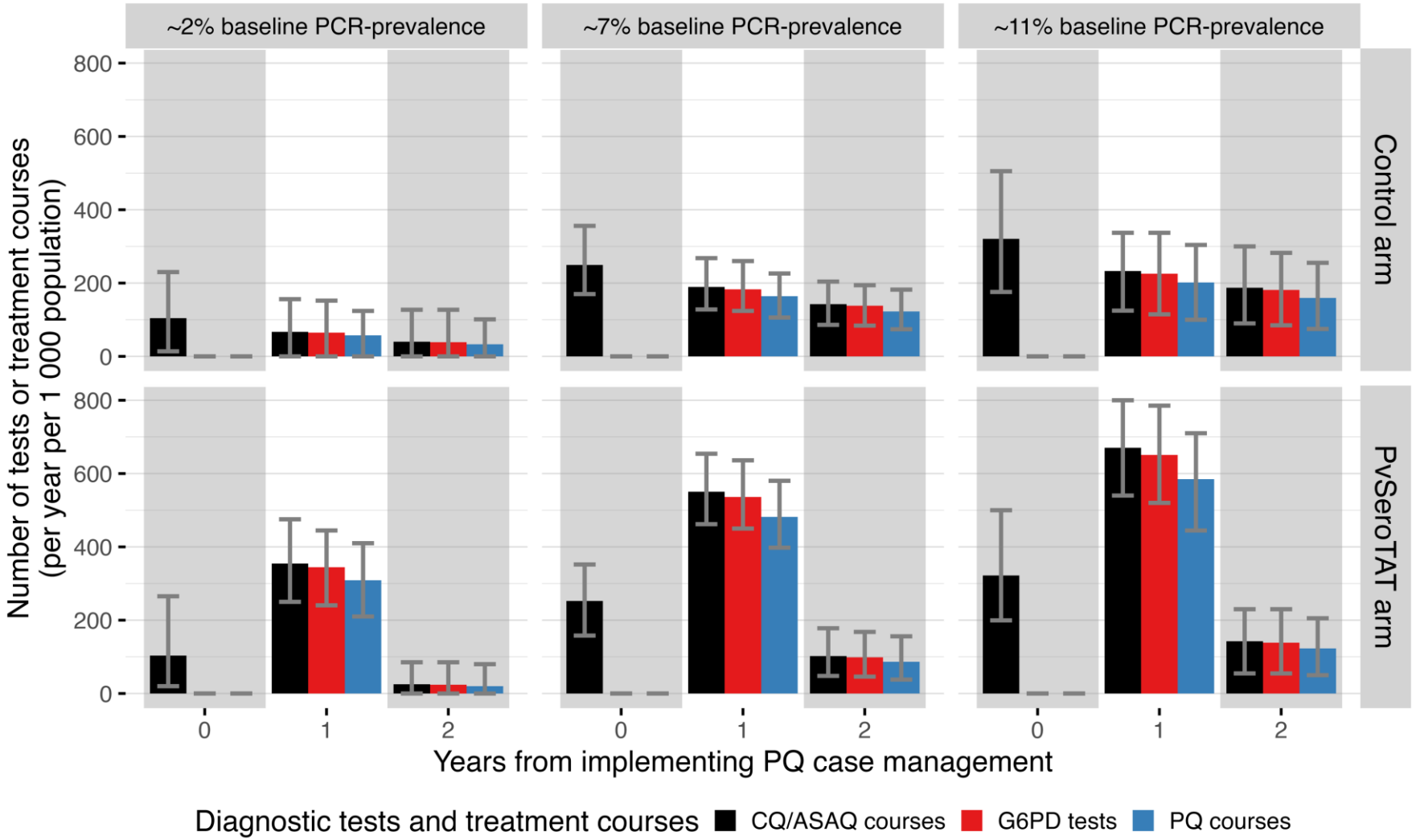
Estimate necessary G6PD tests and drug doses

Question
How many G6PD tests and drug doses are needed and when?

Status
Theoretical simulations

Next steps
Incorporate data
- Weight by age and sex
- Baseline survey

Output
Worst-case scenario for number of G6PD tests and drug doses



Summary and next steps

Summary (part 1)

Estimating per-patient hypnozoiticidal efficacy of PQ and TQ

Effective PQ and TQ can eliminate almost all *P. vivax* hypnozoites

PQ and TQ regimens have differing hypnozoiticidal efficacies

Quantifying population-level impact of radical cure

Systematic barriers hamper population-level impact of radical cure

- PQ adherence
- PQ and TQ eligibility criteria

Population-level impact decreases with increasing transmission intensity

These results will be published in *The Lancet Infectious Diseases*

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Summary (part 2)

Guiding the PvSTATEM cluster-randomised clinical trial

PQ dosage does not significantly impact trial outcome

- PvSTATEM study team has opted for the lower PQ dosage (more cost-effective)

Size and transmission intensity of clusters may impact success of trial

- PvSTATEM study team will not include clusters with low population and/or low transmission

Need in G6PD tests and drug doses can be estimated

- PvSTATEM study team will use worst-case estimates to prepare sufficient consumables
- These estimates will be updated once complete baseline survey data becomes available

ExposUM Fellowship

WP2: Factors influencing the efficacy of antimalarial drugs

- Quantify the potential impact of malaria seasonality on efficacy estimates
  - Simulate trial roll-out
  - Vary transmission seasonality and date of trial onset
  - Compare efficacy estimates
- Refine hypnozoiticidal efficacy estimates
  - Obtain patient-level clinical trial data
  - Update efficacy estimates accounting for seasonality, patients' hypnozoite load, and sex

WP1: Spatio-temporal drivers of respiratory virus transmission

- Identify spatio-temporal drivers for a range of respiratory viruses in France
  - Obtain infection time series and socio-demographic data
  - Compute spatio-temporal regression
- Identify optimal spatio-temporally targeted interventions against SARS-CoV-2
  - Characterise human contact patterns
  - Extend transmission model to include spatio-temporal drivers and contact patterns
  - Validate extended model against data

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Ric Price

London School of Hygiene and Tropical Medicine
Chris Drakeley, John Bradley

Walter + Eliza Hall Institute
Ivo Mueller

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