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Mathematical modeling to optimize cohort monitoring to estimate incidence and time to first infection in malaria field studies

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Introduction

1) Novel malaria interventions are being deployed e.g. dual active-ingredient insecticide-treated nets (2023) and R21 malaria vaccine (2023)
   - ➢ Urgent need for field efficacy evaluations

2) Longitudinal study is the gold standard to evaluate the efficacy/effectiveness of interventions by:
   - Incidence rate
   - Time-to-first infection
   - ➢ No standardized methodology for the real field study design
   - ➢ Also highly depend on the study situation

❑ Biweekly visits may not feasible due to limited resources
❑ Some participants may demand RDT on asymptomatic individuals, especially when blood samples are collected from all participants for PCR.
❑ Some study funds may not support parasite clearance for individuals who test negative on the RDT at enrollment.

Aim

To optimize follow-up and parasite detection strategies based on study-specific issues and regulations under several combinations of the following variables:

Variables	Descriptions
Outcomes	{Case incidence rate, Infection incidence rate, Time to first infection}
RDT testing	{All participants regardless of symptoms, Only those with symptoms}
Follow-up frequency	{Biweekly, Monthly}
Parasite clearance at enrollment	{Clear parasites in all individuals, Clear only RDT positives}
Transmission intensity	Entomological Inoculation Rate (EIR; infectious bites/person/year) {1: low, 10: moderate, 50: high}

Methods

- Using the agent-based malaria transmission model (Figure 1), expanding the established model by Imperial College London *Watson OJ et al., eLife, 2017*
- The model explicitly incorporates:
  - ✓ Heterogeneity in mosquito biting rate
  - ✓ Pre-erythrocytic immunity
  - ✓ Acquired and maternal clinical immunity
  - ✓ Detection immunity

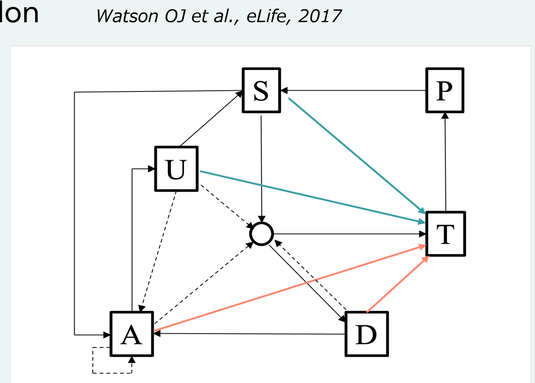

Figure 1: Flow for the human component of the model
S: susceptible, T: treated, D: untreated clinical disease, P: prophylaxis, A: asymptomatic patent, U: asymptomatic sub-patent infection (can be detected by PCR, but not by RDT), Red line: indicating active case detection by cohort monitoring, Blue line: indicating parasite clearance at baseline

- Assumption:
  - ✓ 50% reduction in mosquito bites by a vector control intervention
  - ✓ Among closed populations, 10% in the intervention group, 10% in the control group
  - ✓ In both groups, only children aged 6 months to 14 years old will be followed
  - ✓ After the monitoring starts, treatment seeking rates will increase (40% -> 80%)

- Simulation and analysis
  - ✓ 200 simulations for each scenario by changing: 1) RDT testing, 2) visit frequency, 3) parasite clearance at enrollment, 4) endemicity, and 5) total populations

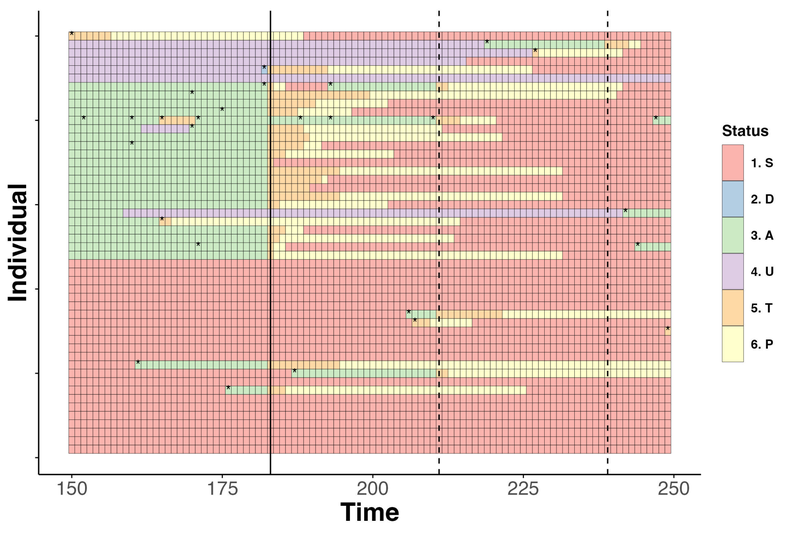

Figure 2: Example of the individual's infection status change in the scenario of 1) RDT for all, 2) Monthly visits, 3) parasite clearance only for RDT positives at enrolment , 4) EIR: 10 , 5) total 3,000 populations.

S: susceptible, T: treated, D: untreated clinical disease, P: prophylaxis, A: asymptomatic patent (can be detected by PCR or RDT), U: asymptomatic sub-patent infection (can be detected by PCR, but not by RDT) *: true infection (bytes by an infected mosquito and get infected), Vertical solid line: the timing of the intervention start and treatment if RDT positive, Vertical dashed line: the timing of cohort visit

- ✓ Power calculation using:
  - ❖ Generalized linear Poisson regression model for incidence outcomes
  - ❖ Cox hazard model for time-to-first malaria infection outcomes

Results

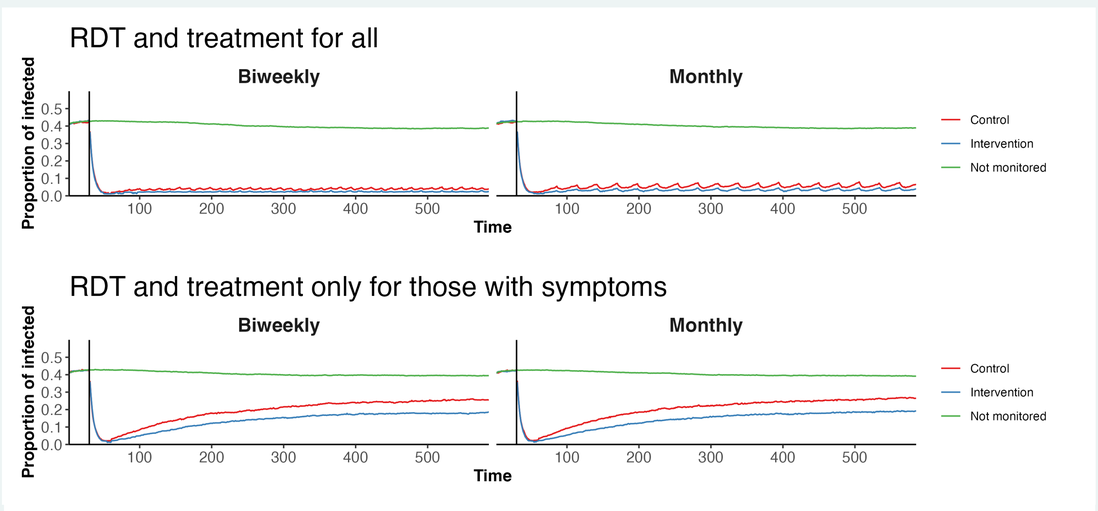

Figure 3: Time trends of the proportion of the infected individuals in each of 4 scenarios with parasite clearance at enrolment and EIR:10 by changing visit frequency and RDT targets.
Vertical solid line: the timing of the intervention start and treatment if RDT is positive

- In RDT for all scenario, substantial reduction of infected proportion even in the control groups after the monitoring starts
- In RDT only for symptomatic scenario, initial parasite clearance substantially lowered the infected proportion, but gradually recovered

Table 1: Estimated outcomes by 200 simulations (median)

		True infection incidence		Infection incidence		Case incidence		Time to first infection	
EIR	Visit	RDT all	RDT symptom	RDT all	RDT symptom	RDT all	RDT symptom	Clear all	Clear RDT positives
10	Biweekly	0.99	1.10	1.05	1.85	0.444	0.448	340	299
10	Monthly	1.00	1.09	0.96	1.49	0.436	0.467	337	302
50	Biweekly	4.51	4.94	3.96	5.08	1.052	1.120	204	171
50	Monthly	4.70	4.80	3.34	4.00	1.055	1.097	206	180

- The true infection incidence rate (IR) were decreased in RDT for all scenarios
- When RDT only for symptomatic, the detected infection IR was overestimated compared to the true IR
- Detected infection IR decreased with longer visit intervals but case IR was not affected by the visit intervals
- Time to first infection got longer if parasites were cleared in all participants

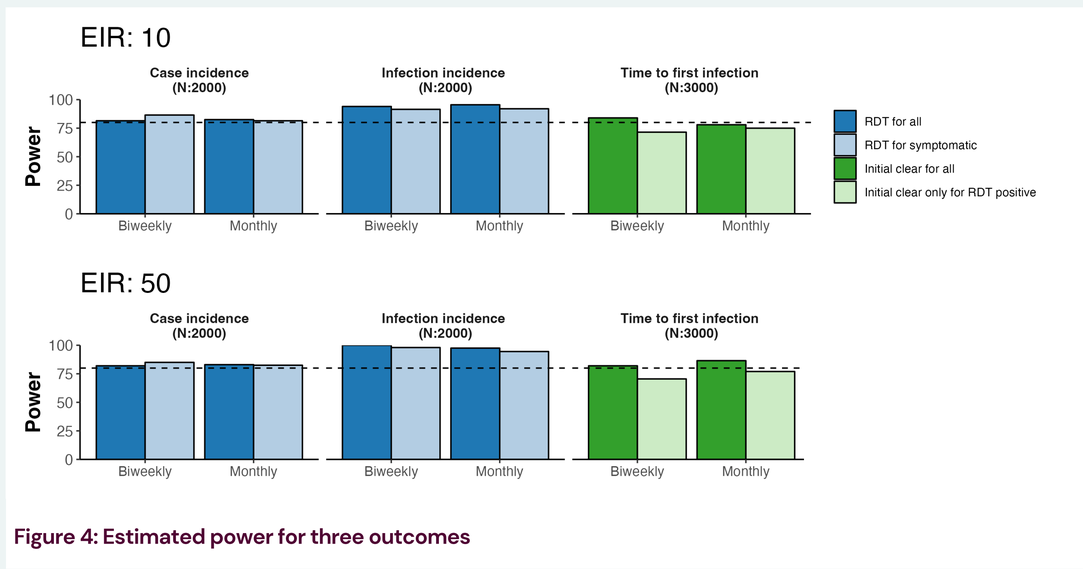

Figure 4: Estimated power for three outcomes

- No difference in power for IR and time to first infection regarding the visit frequency
- Both case and infection IR were not affected by RDT testing
- By parasite clearance for all at enrolment, the power for time to first infection was increased

Summary

- ➢ The infected population decreased by monitoring
  - ✓ Baseline data for sample size calculation should be carefully selected based on study characteristics such as test targets and visit frequency
- ➢ With a sufficient sample size, visit frequency does not affect statistical power
  - ✓ Intensive monitoring, such as biweekly visits, may not always be necessary
- ➢ RDT only for symptomatic overestimate infection incidence by counting untreated asymptomatic PCR positives as new infections
  - ✓ RDT targets should be decided based on primary objectives and field settings
- ➢ Parasites clearance at enrollment affected the power for time to first infection
  - ✓ Lack of parasite clearance at enrollment requires more sample sizes for studies in which the primary outcome is time to first infection

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