RESEARCH

Assessing a primaquine intervention in Cambodia 2020–2025 to control vivax malaria

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Abstract

Background: Elimination targets for *Plasmodium vivax* are approaching, with the Cambodian target 2025. Quantitative tools can help determine if proposed new strategies will be sufficient to meet those targets.

Methods: We calibrated the Optima malaria transmission model reported case data from 2011–2018 for six Provinces with different transmission levels. The model had two human populations: with males 15 years plus, and everyone else. We used the calibrated model to explore for best and worst case interpretations of the available case data, and of the Primaquine intervention.

Results: We found elimination is unlikely to be reached in Provinces with fairly high burdens of *Plasmodium vivax*, such as Pursat, by only targeting adult males with Primaquine. However, it will substantially reduce transmission. As such, we identify how many tests will need to be conducted to have 99% confidence of detecting at least one case, given the lower incidence by 2025.

Conclusions: A primaquine intervention targeting adult males is likely to have a substantial impact on transmission of *P. vivax*, though it is not likely to result in elimination from all Provinces by the 2025 target. The surveillance requirements to ensure the resulting lower incidence is detected as Cambodia approaches elimination may be infeasible, e.g. for Takeo, especially as all Provinces will see a decrease in case counts as the intervention is Nationwide.

Keywords: Malaria; *Plasmodium vivax*; Transmission; Primaquine; Radical cure; Mathematical model

Background

Plasmodium vivax (*P. vivax*) is the cause of a significant burden of malaria globally, with an estimated XX cases, XX deaths [**?**]. In Cambodia, it has been responsible for 30–80% of cases in different Provinces, with the proportion increasing as the burden of *Plasmodium falciparum* (*P. falciparum*) has decreased [**?**].

The key difference between *P. falciparum* and *P. vivax* is the hypnozoite stage of *P. vivax*, which results in relapses [**?**]. There are an estimated XX hypnozoites formed from each infectious mosquito bite, though the biology and mechanisms are poorly understood [**?**]. Standard treatment for *P. vivax* is Chloroquine (CQ) for a blood stage infection. Radical cures have been developed to clear the hypnozoite stage, using 8-Aminoquinolines [**?**]. Primaquine (PQ) has been approved/licenses for use in several countries, though the WHO recommendation is to test for G6PDd before administration [**?**].

Elimination targets for *P. vivax* have been set for many countries [**?**], and the Cambodian target is 2025 [**?**]. Cambodia are currently trialling a 14-day low dose primaquine intervention for adult males in a couple of health centres in Pursat Province. If successful, this will be expanded into a National programme. We use transmission modelling to determine if this is likely to be sufficient to eliminate *P. vivax* by the 2025 target.

Methods

Data synthesis to assess disease burden

Data on malaria incidence were obtained from the Cambodia National Center for Parasitology, Entomology and Malaria Control (CNM) **??**. Population and mortality data were obtained from the Cambodia Bureau of Statistics **??**. The aggregated data used for model calibration are provided in Additional file **??**, and on GitHub at https://github.com/rihickson/vivax-primaquine-Cambodia.

Make this repo public.

Epidemic model

The dynamic transmission model of *P. vivax* is based on that by Scott *et al.* [**?**]. It accounts for transmission between humans and mosquitoes, with the conceptual disease progression in the model depicted in Fig **??**. People in the model are identified as: susceptible; infected with *P. vivax* in the liver only (hypnozoites

and/or active liver stage); infected with active blood stage infection able to infect mosquitoes (gametocytes present – further divided into clinical, severe, or asymptomatic); or recovered and immune (with no hypnozoites). The recovered and immune compartment is important for capturing *P. vivax* dynamics given our current understanding of the importance of immunity in reducing transmission or symptomatic infections []. The human population is stratified into males 15 years and older (M15+) and everyone else (Gen), to enable the primaquine intervention proposed in Cambodia to be captured by the model. Further details on the full model structure, parameter values, and calibration are provided in Additional file **??** and on [Github]https://github.com/rihickson/vivax-primaquine-Cambodia.

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Programmatic response considered

For the sake of <fancy word meaning simplicity of model design>, the only explicit programmatic response considered is the primaquine intervention. The effect of all other interventions are considered to be captured by the model calibration (see §).

The PQ programmatic response is considered to have four key parameters: start date (October 2020), coverage (c), G6PD RDT sensitivity (G), and the effectiveness of PQ in terms of hypnozoite removal (E: a combination of efficacy and adherence). The PQ scenario has, from the start date, $(1-c)(1-G)(1-E)$ times the proportion of the population successfully completing treatments not clearing hypnozoites. The baseline scenario has no PQ, and a default value of 0.75 of the population not clearing hypnozoites on successful treatment completion. To determine if elimination of *P. vivax* is possible by the target date, we consider the case where there is 1.0 coverage, no G6PD deficiency (1.0 of the population are eligible for PQ), and 1.0 effectiveness of PQ, meaning after treatment there are no M15+ with hypnozoites. This is beyond a "best case scenario", as these numbers are not achievable. Hence, if *P. vivax* is still present in 2025 in the model predictions, this additional intervention alone will not be sufficient.

though this is actually more like the proportion of the population who are G6PD¿0.7 atm, and hence eligible for PQ

Model calibration

Data on annual incidence (2011–2018), testing numbers, and demographics were used to calibrate the model for each population stratification and Province (see Additional file **??**: Figures **??**–**??**).

The population size was modelled in each Province by group, including transitions from the general population (Gen) to adult males (M15+). The population model (births, deaths, and transitions) was calibrated to fit the known demographics of each Province. I.e. estimated population size, known age and gender breakdown, and expected national lifespan.

The incidence data was divided into 6 clusters by positive *P. vivax* test results in 2018, and a Province was chosen at random from each cluster. Provinces where the borders had changed during 2011–2018 were excluded from being chosen. Except that Pursat was not randomly selected but deliberately chosen, since this is where the trials are currently being conducted. The other five Provinces considered are: Mondul Kiri, Kampong Chhnang, Battambang, Pailin, and Takeo.

The model was calibrated to the incidence and test data using parameters for the relative susceptibility of the population group to malaria infection; the probability of developing malaria-like symptoms for each person in a given year; the daily probability of testing for people with non-severe malaria-like symptoms such as fever; the daily probability of testing for people with severe malaria-like symptoms; the duration of the latent period (i.e. until hypnozoite reactivation); the proportion incompletely clearing hypnozoites after naturally recovering; and the proportion of new malaria cases that are asymptomatic (see Additional file **??**: Table **??**). To allow for changes in the surveillance system in Cambodia (see, for example, [**?**]), and changes in the other interventions through time, we calibrated to a "best case" and "worst case" baseline incidence scenario. The "worst case" is for the true incidence to be around the higher values of the data and increasing, and the "best case" is for the true incidence to be around the lower values of the data and decreasing. The true values are likely inbetween, but this enables us to capture the extreme ends. Uncertainty bounds on the model prediction were generated by sampling ±10% of the calibrated parameter values for 30 iterations, and represent 75% of the subsequent range.

Surveillance

Given the expected substantial impact on transmission from providing PQ to M15+, we use a negative binomial to estimate how many tests would need to be conducted to be 0.99 confident of detecting at least one case, assuming 100% sensitivity and

specificity of the tests. We also use a binomial to identify the probability of detecting at least one case (assuming 100% sensitivity and specificity) as the number of tests conducted changes, for the predicted incidence of *P. vivax* in 2020 and 2025. The difference in particular is then indicative of considerations that will need to be given to existing surveillance to be confident that elimination has been reached.

Results

Current burden of disease in Cambodia

Model calibration and validation

Primaquine impact on burden of disease in Cambodia

Discussion

Conclusions

List of abbreviations

Cambodia National Center for Parasitology, Entomology and Malaria Control (CNM)

CQ = Chloroquine

P. vivax= *Plasmodium vivax*

P. falciparum= *Plasmodium falciparum*

PQ = Primaquine

Competing interests

The authors declare that they have no competing interests.

Author's contributions

PN, RIH, RMH, AD, DJP and JMM conceived of the project and oversaw the design. PN and RIH curated the data. RMH and RIH developed the transmission model and code implementation, and calibrated the model. RIH, DJP, JMM wrote the surveillance decision support model. RIH, RMH, DJP, AD, JAS, FJIF, JMM, PN prepared the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1 Model calibration for Mondul Kiri. Number of malaria cases as a function of time, from 2011 to 2025. A) General population for the high and increasing baseline incidence. B) Males 15 years and older population for the high and increasing baseline incidence. C) General population for the low and decreasing baseline incidence. D) Males 15 years and older population for the low and decreasing baseline incidence.

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Tables

Additional Files

Additional file 1 — Sample additional file title

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Additional file 2 — Sample additional file title

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Table 1 Surveillance targets for 0.99 probability of detecting at least one case of *P. vivax*in a Province, given the scenarios outlined in § , assuming 100% sensitivity and specificity of the tests (so a lower bound on number of targets).

Year		2020				2025			
Scenario	Incidence	Low	Low	High	High	Low	Low	High	High
	Primaquine	None	M 15+	None	M 15+	None	M 15+	None	M 15+
Province	Pursat	441	444	2,345	76	76	557	2,610	70
	Mondul Kiri	172	173	48	48	280	1,388	54	263
	Kampong Chhnang	3,798	3,819	649	653	5,564	26,094	614	2,998
	Battambang	2,962	2,978	433	436	3,916	19,191	384	1,922
	Pailin	850	855	123	124	1,040	4,960	122	579
	Takeo	14,335	14,415	2,345	2,358	18,905	89,418	2,205	10,919