Is a radical cure enough? Assessing a primaquine treatment for adult males in Cambodia to eliminate vivax malaria by 2025

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Research Article

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Is a radical cure enough? Assessing a primaquine treatment for adult males in Cambodia to eliminate vivax malaria by 2025

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Abstract

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

Methods: We calibrated the Optima Malaria transmission model to reported case data from 2011–2018 for six provinces with different transmission levels. The model had two human populations: males aged 15 years and older, and everyone else. We assessed the addition of the new low-dose primaquine intervention (0.25 mg/kg daily x 14 days) for diagnosed *P. vivax* infections where males aged 15 years and older were prescribed primaquine after testing glucose-6-phosphate-dehydrognase normal to the 2018 status quo (blood-stage treatment only). Results were evaluated over stochastic iterations of the calibrated compartmental model, incorporating best and worst case interpretations of the available case data given uncertainty over underlying *P. vivax* incidence in 2020.

Results: Under 2018 status quo conditions in the absence of primaquine radical cure, we found that *P. vivax* elimination would be unlikely to be achieved by 2040 in any province. Elimination by 2025 was not projected in any province even with best case assumptions for primaquine intervention coverage, G6PD-based eligibility, and primaquine efficacy; however, we estimated that the addition of the primaquine intervention could reduce *P. vivax* transmission by 67%-83% by 2025. We found that sustained application of the primaquine intervention was likely to result in elimination by 2040 in all six provinces with best case estimated baseline incidence, and in the two lowest incidence provinces with worst case baseline incidence.

Conclusions: Without additional novel interventions, the primaquine radical cure (0.25 mg/kg daily x 14 days targeting adult males with diagnosed *P. vivax* infections) is not projected to result in elimination from any province by the 2025 target even under the most optimistic interpretation of the available case data. However, the implementation of a primaquine intervention in Cambodia is likely to have a substantial impact on transmission of *P. vivax* and may make elimination feasible over the longer term.

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

*Plasmodium vivax* is the cause of a significant burden of malaria globally, with an estimated 14.3 million cases in 2017 [1]. Cambodia has reported no malaria deaths since 2018 [2], but with the rise of artemisinin-resistant *Plasmodium falciparum* in Cambodia, the relative burden of *P. vivax* has increased due to increased focus on eliminating *P. falciparum*. *P. vivax* is now responsible for 30–90% of cases across the provinces in Cambodia [2, 3, 4]. Artemisinin combination therapy (ACT) is the standard treatment for blood-stage malaria infection in Cambodia, but this treatment does not clear the dormant liver parasites, called hypnozoites. The hypnozoite stage of *P. vivax* results in relapses [5, 6], and is a key difference between *P. falciparum* and *P. vivax*. Since an estimated 79% of *P. vivax* episodes are due to relapse, targeting the hypnozoite reservoir with radical cure is considered a key element of control [7, 8].

The only widely available drug for radical cure is primaquine (PQ). The World Health Organization (WHO) recommendation is to test for G6PD deficiency before administration of PQ where possible, in order to avoid the primaquine-induced haemolysis that can result in those with this enzymopathy [9]. G6PD deficiency is measured by enzymatic activity, and a value of less than 30% is considered severe deficiency. Since G6PD deficiency is x-linked, females may be homozygous or heterozygous. The latter is more challenging to detect as some will have intermediate activity (30–70%) and still be at risk of severe haemolysis [10].

The WHO defines malaria elimination as “interruption of local transmission (reduction to zero incidence of indigenous cases) of a specified malaria parasite in a defined geographical area as a result of deliberate activities.” [11]. The elimination target for *P. vivax* in Cambodia is 2025 [12]. PQ has been recommended as a radical cure for *P. vivax* in the National Treatment Guidelines for Malaria since 2012 [13], but practical adoption of PQ as a first-line treatment has been hampered by historical complications resulting from use of PQ as part of mass drug administration in Cambodia [14]. In November 2019, Cambodia began trialling the use of a 14-day low-dose PQ (0.25 mg/kg) intervention for adult males with a diagnosed *P. vivax* infection testing G6PD normal with qualitative G6PD rapid diagnostic tests (RDTs) in two health centres in Pursat province [15], and has since rolled this out as part of the national programme (Table 1). Ongoing policy changes to safely im-
<table>
<thead>
<tr>
<th>Type of test/treatment</th>
<th>Timeline</th>
<th>Geographical area</th>
</tr>
</thead>
</table>
| G6PD qualitative test (CareStart)+ PQ14 for males 20kg | Sep. 2019 – training  
Oct 2019 – distribution of tests  
Nov. 2019 – started trial  
Dec. 2020 – ended trial | 4 pilot provinces |
| G6PD quantitative test (SD Biosensor)+ PQ14 for all 20kg+ | Oct. to Nov. 2020 – training  
Jan. 2021 – distribution of tests  
Feb. 2021 – started implementation | Whole country |

Table 1: Trial and implementation timeline of the primaquine intervention in Cambodia

implement the effective radical cure for \textit{P. vivax} in Cambodia are an important part of the regional strategy malaria elimination strategy [16].

We used transmission modelling to inform the planning process of the Cambodia National Center for Parasitology, Entomology and Malaria Control (CNM) in early 2020 to determine if low-dose PQ for M15+ would be likely to be sufficient to eliminate \textit{P. vivax} by the 2025 target.

\section*{Methods}

\subsection*{Data sources and synthesis}

Demographic data, including mortality, were obtained from the National Institute of Statistics in Cambodia [17]. The demographic data was from the 2008, 2013, and 2019 census [17], including estimated population size, known age and gender breakdown, and life expectancy.

Malaria case data were obtained from the CNM. The raw data included total number of tests, and numbers of positive tests by parasite species, test type (microscopy or Deepstick, a rapid diagnostic test), province, and week of test. Additionally, population stratification for estimated \textit{P. vivax} incidence was provided as a proportion of cases by age and sex, from January 2015–November 2019. Subsequently, the raw data for each province was pro rated to achieve the correct proportion of cases for males 15 years and older (M15+), since they are the target sub-population for the PQ intervention.

\subsection*{Epidemic model}

The dynamic transmission model of \textit{P. vivax} is based on that by Scott \textit{et al.} [18] used to model \textit{P. falciparum}. It is a compartmental model that accounts for trans-
mission between humans and mosquitoes, with the disease progression in the model depicted in Fig 1 including adjustments to account for *P. vivax* further detailed in the Supplemental appendix. The model includes compartments for humans encapsulating disease states: “Susceptible”; “Latent” infected with *P. vivax* in the liver only (hypnozoites and/or active liver stage); “Active” infected with active blood-stage infection able to infect mosquitoes (gametocytes present), further divided into exposed (during incubation prior to symptoms), uncomplicated or clinical, severe (rare in *P. vivax* infections but present in low numbers in case data for Cambodia), and asymptomatic (including chronic malaria and natural resistance from prior exposure); or “Recovered/immune” (with no hypnozoites). Each model compartment without active malarial symptoms (susceptible, latent, and asymptomatic) is stratified to include the possibility of non-malarial fevers, screening, and the potential for false-positive treatment as a result. 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 [19].

The human population is stratified into M15+ and everyone else (Gen), to enable the PQ intervention proposed in Cambodia to be captured by the model. To capture the possibility of elimination, the model was run with stochastic transitions between compartments, based on the probability of each individual transitioning during each 5-day timestep.

![Optima Malaria model diagram](image)
Model calibration

Data on annual incidence (2011–2018), testing numbers, and demographics were used to calibrate the model for each population stratification (i.e. M15+ and Gen) and province.

The population size was modelled in each province by group, including transitions from Gen to M15+ to represent aging of male children. The population model (births, deaths, and transitions) was initialized to match reported population sizes in 2011 and calibrated to fit the demographics of each province to 2019, based on the National Institute of Statistics in Cambodia data [17].

The case data was divided into 6 clusters by positive *P. vivax* test results in 2018, as shown in Table 2, and a province was chosen at random from each cluster to generate a representative selection of *P. vivax* incidence levels across provinces. Pursat was deliberately chosen in keeping with the first PQ trial location. Provinces where the borders had changed during 2011–2018 were excluded from being chosen to ensure consistency of reported data. In addition to Pursat, the other five provinces selected for our analyses were Mondulkiri, Kampong Chhnang, Battambang, Pailin, and Takeo.

The following key model parameters with substantial uncertainty were calibrated to fit the incidence and test data using parameters based on deterministic modelling of transmission (e.g. with fractional transfers of a proportion of the population in a model compartment, rather than stochastic transfers of individuals between model compartments):

- the relative susceptibility of the population group to malaria infection given prevailing local conditions (unitless, with M15+ being 7 to 11-times more susceptible than Gen);
- the rate of developing malaria-like symptoms for each person in a given year for reasons other than malaria (ranging from less than 0.01 to 0.15 in M15+ by province, with higher values historically);
- the daily rate of testing for people with non-severe malaria-like symptoms such as fever (0.03, representing a 26% probability of testing within the median 10 day symptomatic duration);
<table>
<thead>
<tr>
<th>Cluster</th>
<th>Province</th>
<th>Pro rata 2018 P. vivax cases</th>
<th>2018 Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>5000+</td>
<td>Pursat</td>
<td>9,245</td>
<td>411,759</td>
</tr>
<tr>
<td>3000–5000</td>
<td>Preah Vihear</td>
<td>4,092</td>
<td>251,352</td>
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<td></td>
<td>Kampong Speu</td>
<td>3,569</td>
<td>872,219</td>
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<td></td>
<td>Mondulkiri</td>
<td>3,464</td>
<td>88,649</td>
</tr>
<tr>
<td></td>
<td>Stung Treng</td>
<td>3,204</td>
<td>159,565</td>
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<tr>
<td>1000–3000</td>
<td>Kratie</td>
<td>2,518</td>
<td>372,825</td>
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<tr>
<td></td>
<td>Ratanakiri</td>
<td>2,214</td>
<td>204,027</td>
</tr>
<tr>
<td></td>
<td>Kampong Chhnang</td>
<td>1,956</td>
<td>525,932</td>
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<td></td>
<td>Kampong Cham</td>
<td>1,774</td>
<td>895,763</td>
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<td></td>
<td>Oddar Meanchey</td>
<td>1,376</td>
<td>261,252</td>
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<tr>
<td>500–1000</td>
<td>Siem Reap</td>
<td>853</td>
<td>1,006,512</td>
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<tr>
<td></td>
<td>Battambang</td>
<td>783</td>
<td>987,400</td>
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<td>Kampong Thom</td>
<td>765</td>
<td>677,260</td>
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<td>Kampot</td>
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<td>120–500</td>
<td>Preah Sihanouk</td>
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<td>302,887</td>
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<td></td>
<td>Takeo</td>
<td>281</td>
<td>899,485</td>
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<td></td>
<td>Koh Kong</td>
<td>190</td>
<td>123,618</td>
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<td>Phnom Penh</td>
<td>143</td>
<td>2,129,371</td>
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<tr>
<td>0–120</td>
<td>Prey Veng</td>
<td>115</td>
<td>1,057,428</td>
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<td>Kandal</td>
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<td>Pailin</td>
<td>101</td>
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<td>Banteay Meanchey</td>
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<td>Kep</td>
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<td></td>
<td>Svay Rieng</td>
<td>22</td>
<td>524,554</td>
</tr>
</tbody>
</table>

Table 2: Clustering of provinces by pro rated reported 2018 *P. vivax* case numbers, with modelled provinces highlighted.
• the daily rate of testing for people with severe malaria-like symptoms (0.15, representing an 80% probability of testing within the median 10 day symptomatic duration); and
• the average duration of the latent period (i.e. until hypnozoite reactivation) (76 days, capturing a lower limit of approximately three weeks as reported for Cambodia [20] as well as the potential for some much longer individual durations);
See the Supplementary appendix for additional parameterization and calibration details. To allow for changes in the surveillance system in Cambodia, and changes in the other interventions through time, we calibrated to both a “high” and a “low” baseline incidence scenario. The “high” scenario is for the true incidence to be consistent with the reported 2018 *P. vivax* incidence data, with a projection of increasing incidence based on the historically lower reported case data relative to 2018, and the “low” scenario is for the true incidence to be consistent with the historical values prior to 2018 and following the decreasing trend within those values. The true values for incidence very likely lie within this range, and our approach enables us to capture both the best and worst case baseline scenario for elimination. Uncertainty bounds on the model results were generated by sampling within ±10% of the calibrated parameter values and running with stochastic transmission of malaria over repeated iterations, with rejection and replacement of any samples outside of ±50% of the calibrated 2018 value of malaria cases due to the wide uncertainty on those values in either scenario. Based on qualitatively identical model runs from two different random seeds with 100 iterations with no more than ±10% in the proportion of scenarios reaching elimination by 2040 in each province, a final independently seeded run was conducted with 300 iterations. Uncertainty bounds represent 95% of the subsequent range.

**Primaquine intervention**

In order to directly estimate the impact of 14-day low-dose PQ (0.25 mg/kg daily, defined in the Cambodian national treatment guidelines as standard-dose to differentiate from the lower dose used as transmission blocking for *P. falciparum* [13]) use in M15+ with diagnosed *P. vivax* infections, this is the only programmatic response explicitly considered in the model. The effect of all other interventions that were in
use during and prior to 2018 are considered to be captured by the model calibration, and include testing and treatment, the distribution of long-lasting insecticidal nets, malaria education to households, early diagnosis and treatment programs through case finding, case management and reporting, and complementary activities supported by civil society organizations in support of malaria elimination [21]. More than 75% of malaria cases reported between January 2015 and November 2019 in CNM malaria case data were in the M15+ population, so best case coverage of the PQ intervention has the potential to reach a large portion of malaria cases.

Four key parameters describe the PQ programmatic response: the start date of October 2020 ($D$), coverage ($c$), eligibility for PQ based on the proportion of males with diagnosed $P.\ vivax$ infections who are tested as G6PD normal incorporating RDT sensitivity ($G$), and the effectiveness of PQ in terms of hypnozoite removal ($E$: a combination of efficacy and adherence). The baseline scenario has no PQ, and a default proportion of 0.75 of the population not clearing hypnozoites on successful schizonticidal treatment completion [7]. Therefore, from the start date, for each member of the population successfully completing treatment has a probability of not clearing hypnozoites equal to $0.75(1 - c)(1 - G)(1 - E)$ with this equation incorporating attainable coverage, G6PD eligibility, and effectiveness of PQ respectively. To determine if elimination of $P.\ vivax$ is possible by 2025, we consider the implementation of three scenarios from October 2020 until December 31 2040.

**2018 status quo** is the baseline with no practical application of a radical cure and a continuation of standard of care interventions targeting the elimination of $P.\ falciparum$ of December 2018 in the most recently reported data at the initiation of this analysis. Standard of care interventions on model parameters relating to malaria transmission, diagnosis, and treatment were captured as part of the status quo calibration and not individually modelled.

**Best case primaquine males 15+** includes the best case for each parameter estimated to be achievable with 90% coverage of testing, 90% eligibility based on G6PD normal results (it has been estimated that prevalence of G6PD deficiency among M15+ ranges from 5% to 15% in different regions of Cambodia [22, 23]), and 88% efficacy in clearing hypnozoites in those who complete treatment [7]. This is beyond what was achieved through pilot implementation of G6PD RDTs in 4 provinces, where 45% of adult males with diagnosed $P.\ vi-$
vax and mixed infections were tested for G6PD deficiency, with 76% of those tested being G6PD normal, and 78% of those completing the 14-day treatment [24]. Although opportunities to increase coverage, improve testing, and increase adherence were identified from this pilot, if *P. vivax* is still present in 2025 in the model results for this best case scenario, PQ in M15+ alone will not be sufficient for elimination.

**Perfect radical cure** is a beyond best case scenario in which a perfect (100% success rate) radical cure is available as part of treatment to 100% of all diagnosed *P. vivax* cases, with no eligibility constraints based on gender, age, weight, or G6PD deficiency. This scenario captures any future expansion of eligibility or treatment effectiveness.

**Evaluation of primaquine impact**

Indigenous cases in keeping with the WHO definition of malaria elimination [11] are captured in the model as new malaria cases (whether symptomatic or asymptomatic) occurring in the susceptible population, excluding relapse cases in people with existing latent *P. vivax* infections. We also evaluate the projected number of diagnosed *P. vivax* cases, and the total burden of people with *P. vivax* parasites present including latent infections, to evaluate how these change over time within each scenario.

As we conducted stochastic modelling with 300 runs, we can analyse the proportion of runs in which elimination is projected to occur under each scenario in each province with each calibration.

**Results**

**Model calibration**

For each of the 6 provinces, calibrations such as that shown in Fig 2 for Pursat were conducted. The solid red line represents the “worst case” baseline incidence calibration, where the model is calibrated deterministically to the higher data values and increasing trend after 2018 for the M15+ and Gen population groups. The solid blue line represents the “best case”, where the model is calibrated to the lower values and has a decreasing trend. Faint lines show each individual sampled model iteration run as a baseline for each intervention scenario. The remaining province calibrations are shown in Figs 6–10.
Figure 2: Calibration to reported *P. vivax* cases in Pursat. Faint lines represent sampled model trajectories for each of the low and high incidence calibrations. The left column (a) represents the “males 15 years and older” (M15+) population group, and the right column (b) the “everyone else” (Gen) group.

Primaquine impact on burden of disease in Cambodia

The impact of each radical cure scenario from October 2020, is shown in Fig 3 for Pursat. The left column (a, c) represents the median projected number of new indigenous cases of *P. vivax* in Pursat from 300 iterations of each scenario, while the right column (b, d) represents the median projected number of total *P. vivax* cases including relapse in Pursat from 300 iterations of each scenario. The top row (a, b) represents the high incidence calibration, while the bottom row (c, d) represents the low incidence calibration. The projected impact of the *P. vivax* radical cure scenarios for the remaining provinces are shown in Figs 11–15.

While the status quo scenario did not project *P. vivax* elimination by 2025 in any provinces, the best case implementation of PQ for M15+ has a substantial impact on projected case numbers for *P. vivax* in every province (Figure 3, Table 3). PQ is not expected to result in achieving elimination by 2025 in more than 50% of model trajectories in any province, but as seen in Table 4, PQ is projected to result in a 67%–83% reduction in *P. vivax* case numbers by 2025. Conversely, the absence of a radical cure is projected to result in a continuation of calibrated trends prior to 2018, with a 1%–14% increase in case numbers by 2025 in the high baseline incidence scenarios, or a 23%–37% reduction in the low baseline incidence scenarios. In the high baseline incidence scenarios, a perfect radical cure able to be
Province 2019 estimated indigenous cases 2025 projected indigenous cases without radical cure 2025 projected indigenous cases with best case PQ 2025 projected indigenous cases with perfect radical cure

<table>
<thead>
<tr>
<th>Province</th>
<th>Pursat high</th>
<th>Pursat low</th>
<th>Mondulkiri high</th>
<th>Mondulkiri low</th>
<th>Kampong Chhnang high</th>
<th>Kampong Chhnang low</th>
<th>Battambang high</th>
<th>Battambang low</th>
<th>Takeo high</th>
<th>Takeo low</th>
<th>Pailin high</th>
<th>Pailin low</th>
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</thead>
<tbody>
<tr>
<td>2019</td>
<td>2,431 (1,462, 3,739)</td>
<td>2,524 (1,149, 4,661)</td>
<td>713 (264, 1,515)</td>
<td>555 (201, 1,250)</td>
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<tr>
<td>2025</td>
<td>440 (278, 681)</td>
<td>292 (137, 639)</td>
<td>81 (28, 264)</td>
<td>59 (16, 234)</td>
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<td></td>
<td>777 (516, 1,107)</td>
<td>797 (403, 1,373)</td>
<td>211 (68, 723)</td>
<td>186 (48, 641)</td>
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<td>215 (135, 327)</td>
<td>145 (67, 290)</td>
<td>38 (9, 124)</td>
<td>32 (7, 115)</td>
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<td>360 (244, 574)</td>
<td>395 (205, 879)</td>
<td>117 (47, 268)</td>
<td>89 (31, 236)</td>
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<td>62 (35, 100)</td>
<td>38 (14, 92)</td>
<td>11 (3, 30)</td>
<td>8 (1, 25)</td>
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<td>1,030 (669, 1,607)</td>
<td>1,060 (502, 2,176)</td>
<td>269 (83, 856)</td>
<td>217 (57, 775)</td>
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<td>150 (90, 241)</td>
<td>87 (38, 212)</td>
<td>24 (5, 95)</td>
<td>18 (3, 90)</td>
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<td>176 (112, 282)</td>
<td>183 (85, 426)</td>
<td>52 (18, 129)</td>
<td>39 (11, 103)</td>
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<td>28 (7, 67)</td>
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</tbody>
</table>

Table 3: Projected annual *P. vivax* case numbers by province in 2019 baseline and in 2025 under each radical cure scenario. Median of 300 model trajectories (10th percentile, 90th percentile) as of the respective year.

<table>
<thead>
<tr>
<th>Province</th>
<th>Pursat high</th>
<th>Pursat low</th>
<th>Mondulkiri high</th>
<th>Mondulkiri low</th>
<th>Kampong Chhnang high</th>
<th>Kampong Chhnang low</th>
<th>Battambang high</th>
<th>Battambang low</th>
<th>Takeo high</th>
<th>Takeo low</th>
<th>Pailin high</th>
<th>Pailin low</th>
</tr>
</thead>
<tbody>
<tr>
<td>2025</td>
<td>-3% (-26%, 25%)</td>
<td>70% (53%, 84%)</td>
<td>77% (60%, 89%)</td>
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Table 4: Projected percentage reduction in *P. vivax* case numbers by province by 2025 relative to 2019 under each radical cure scenario, relative to status quo for the same underlying parameter sample. Median of 300 sampled model trajectories (10th percentile, 90th percentile) as of 2025.
Figure 3: PQ intervention for *P. vivax* in Pursat. Lines represent annual medians for each individual year from 300 sampled model trajectories given the status quo and each radical cure scenario. Vertical dashed line is the December 2025 elimination target for *P. vivax*.

given to the entire population as treated for *P. vivax* was estimated to result in *P. vivax* elimination by 2040 in more than 50% of model trajectories in Takeo and Pailin - the two lowest incidence provinces.

Figs 4–5 show the proportion of model trajectories in which *P. vivax* elimination was achieved by 2025, 2030, 2035, or 2040, given a baseline calibration to low or high historical estimates of incidence respectively. Over the longest time frame considered, best case PQ increased the average proportion of model trajectories across provinces in which elimination was achieved in the high baseline incidence scenario by 2040 from 0% to 26%, or 42% with a perfect radical cure. In the low baseline incidence scenario, best case PQ increased the average proportion of model trajectories across provinces in which elimination was achieved by 2040 from 4% to 70%, or 77% with a perfect radical cure.
Figure 4: **Timing of elimination under low baseline incidence scenarios** of indigenous transmission of *P. vivax*, according to radical cure coverage achieved *P. vivax*. Proportions of 300 sampled model trajectories in which no indigenous *P. vivax* transmission has occurred for a consecutive period of 3 years at any time prior to December 31 of that year.

Figure 5: **Timing of elimination under high baseline incidence scenarios** of indigenous transmission of *P. vivax*, according to radical cure coverage achieved *P. vivax*. Proportions of 300 sampled model trajectories in which no indigenous *P. vivax* transmission has occurred for a consecutive period of 3 years at any time prior to December 31 of that year.
Discussion

We have used a transmission model to explore the potential impact of prescribing PQ radical cure (0.25 mg/kg daily for 14 days) for diagnosed \textit{P. vivax} cases in M15+ who are tested as G6PD normal, which was a strategy Cambodia was considering for malaria elimination. We found that this strategy is unlikely be sufficient to reach Cambodia’s elimination target date of 2025 in any of the six provinces considered without additional novel interventions. The formal definition of elimination requires there to be no new indigenous transmission after 31 December 2022 in order to achieve three years without indigenous transmission by 31 December 2025 in line with the elimination target. Even under the most optimistic assumptions around baseline \textit{P. vivax} incidence, and beyond best case assumptions of expanded eligibility to all diagnosed \textit{P. vivax} cases and a 100\% efficacy radical cure, elimination was achieved by 2025 in less than 5\% of model trajectories in each province. If baseline incidence is in line with the low baseline incidence scenarios, then elimination by 2030 may be more feasible although still predicted to be achieved in less than 50\% of model trajectories in all provinces.

We have calibrated the Optima Malaria model for six provinces to include malaria interventions introduced prior to and during 2018 in Cambodia targeted primarily at earlier \textit{P. falciparum} elimination, and the success that they also have at reducing indigenous transmission of \textit{P. vivax}. However, without a PQ radical cure, \textit{P. vivax} elimination was not predicted to be achieved even by 2040 in any model iteration in any province under the high baseline incidence scenarios, and not predicted to be achieved by 2040 in any model trajectories for Pursat, or Mondulkiri under the low baseline incidence scenario, with the remaining provinces achieving elimination by 2040 in less than 20\% of model trajectories. Without wide-scale implementation of a radical cure, \textit{P. vivax} is projected to continue in each province of Cambodia.

Conversely, even though we projected that elimination by 2025 would only be achieved in a small minority of model trajectories, elimination over the longer-term appears to be feasible if a PQ intervention for M15+ can be sustained. Because the majority of \textit{P. vivax} cases are in M15+, this best case intervention has qualitatively similar success rates under the low baseline incidence scenarios in achieving elimination by 2040 as a hypothetical perfect radical cure.
As far as we are aware, there have been no other modelling studies answering the question of elimination of *P. vivax* through a PQ intervention for M15+ who are tested as G6PD normal in Cambodia. The transmission model used here contains the flexibility to define the minimal necessary populations and stages of malaria to answer the question posed about reaching elimination by the target date. Furthermore, the Optima Malaria model can be used to evaluate optimal resource allocation to *P. vivax*-targeting malaria interventions as has been applied to *P. falciparum* previously [18].

We have calibrated models for *P. vivax* transmission for six provinces in Cambodia, to high and low baseline incidence scenarios to capture the reasonable bounds of uncertainty arising from limited data and changes in surveillance methods and interventions between 2011 and 2018. By including both a “best case” and a far beyond best case scenario for the implementation of a PQ radical cure, our approach increases confidence in our answer to the posed question: *P. vivax* is not likely to be eliminated by the target date of 2025 in Cambodia through the use of PQ in addition to 2018 status quo interventions for M15+ or even with all populations being eligible. The actual impact under real-world conditions is likely to include lower values for each of coverage, eligibility, and effectiveness as demonstrated in the trial implementation [24] where 29.6% of eligible M15+ completed a radical cure compared with the “best case” value of 71% evaluated here, or 100% in the perfect radical cure scenario.

Future updates to incidence estimates [25] and inclusion of the population-targeted activities and routine use of malaria surveillance data already put into practice by the CNM as part of an “Intensification Plan” which has resulted in reported *P. falciparum/mixed cases* declining by 97.4% between October 2018 and December 2020 [26] may reduce the uncertainty interval from sampled model baselines. As Cambodia now seeks to continue progress in reaching malaria elimination targets, modelling of the combined impact of PQ with other “last mile” interventions could further enhance targeting.

**Conclusions**

We have used transmission modelling to answer a key question for Cambodia posed prior to the implementation of the wider intensification of elimination efforts: will
the use of a PQ radical cure (0.25 mg/kg daily for 14 days) for diagnosed *P. vivax* cases in G6PD normal M15+ from October 2020, in addition to 2018 status quo interventions, be sufficient to eliminate *P. vivax* by the target date of 2025. Given the uncertainties in the case data, we have used a best case scenario approach. We found *P. vivax* is not likely to be eliminated by any province by the target date when only targeting M15+ with low-dose PQ. However, PQ remains a critical intervention, as the absence of a radical cure means *P. vivax* elimination is unlikely to be achieved in this setting over any time frame. PQ is projected by this model to have a substantial impact, on both blood-stage infections (clinical and asymptomatic) and the hypnozoite reservoir. While the addition of low-dose PQ for *P. vivax* treatment alone may not result in elimination by the target date, we project that sustained application of effective PQ may result in the elimination of *P. vivax* by 2040 or earlier, and this evidence may help guide the need for either additional interventions or a change in target date.

**List of abbreviations**

- **CNM** Cambodia National Center for Parasitology, Entomology and Malaria Control
- **P. vivax** *Plasmodium vivax*
- **P. falciparum** *Plasmodium falciparum*
- **ACT** Artemisinin Combination Therapy
- **PQ** Primaquine
- **M15+** Males, 15 years of age and older
- **Gen** Females, 15 years of age and older, and all children under 15 years

**Declaration**

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This work is supported in part by the Australian Centre for Research Excellence in Malaria Elimination (ACREME), funded by the Australian National Health and Medical Research Council of Australia (NHMRC) (1134989). ACREME funded the salary of RIH, data curation from PN and SS. JAS is funded by an NHMRC Investigator Grant (1196068) and FJIF by a NHMRC Career Development Fellowship (1166753). AD is supported by Department of Foreign Affairs and Trade (DFAT) and NHMRC (1132975).

**Availability of data and materials**

National malaria surveillance data available at [https://mis.cnm.gov.kh/](https://mis.cnm.gov.kh/). The aggregated data used to conduct this analysis, as well as the code used to run the model and generate results are available on GitHub at [https://github.com/rihickson/vivax-primaquine-Cambodia](https://github.com/rihickson/vivax-primaquine-Cambodia).

**Acknowledgements**

Not applicable.

**Author information**

Authors and affiliations

Burnet Institute, Melbourne, Australia.
Contributions
PN, RIH, RMH, AD, DJP, and JMM conceived of the project and oversaw the design. PN, SS, and RIH curated the data. RMH, RIH, and RA developed the transmission model and code implementation, and calibrated the model. RIH, DJP, JMM wrote the surveillance decision support model. RIH, RMH, AD, and DJP prepared the manuscript. JAS, KT, JMM, FJIF, NS, RA, SS, and PN reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

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References
2. World Health Organization: World Malaria Report 2021


### Additional File 1 — Supplementary Appendix

Detailed descriptions of the model, data, and calibration are provided in the Supplementary appendix.

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**Figure 6:** Calibration to reported *P. vivax* cases in Mondulkiri.

Faint lines represent sampled model trajectories for each of the low and high incidence calibrations.
Figure 7: **Calibration to reported *P. vivax* cases in Kampong Chhnang.** Faint lines represent sampled model trajectories for each of the low and high incidence calibrations.

Figure 8: **Calibration to reported *P. vivax* cases in Battambang.** Faint lines represent sampled model trajectories for each of the low and high incidence calibrations.

Figure 9: **Calibration to reported *P. vivax* cases in Takeo.** Faint lines represent sampled model trajectories for each of the low and high incidence calibrations.
Figure 10: Calibration to reported *P. vivax* cases in Pailin. Faint lines represent sampled model trajectories for each of the low and high incidence calibrations.

Figure 11: PQ intervention for *P. vivax* in Mondulkiri. Lines represent annual medians for each individual year from 300 sampled model trajectories given the status quo and each radical cure scenario. Vertical dashed line is the December 2025 elimination target for *P. vivax*. 
Figure 12: PQ intervention for *P. vivax* in Kampong Chhnang. Lines represent annual medians for each individual year from 300 sampled model trajectories given the status quo and each radical cure scenario. Vertical dashed line is the December 2025 elimination target for *P. vivax*. 
Figure 13: PQ intervention for *P. vivax* in Battambang. Lines represent annual medians for each individual year from 300 sampled model trajectories given the status quo and each radical cure scenario. Vertical dashed line is the December 2025 elimination target for *P. vivax*. 
Figure 14: PQ intervention for *P. vivax* in Takeo. Lines represent annual medians for each individual year from 300 sampled model trajectories given the status quo and each radical cure scenario. Vertical dashed line is the December 2025 elimination target for *P. vivax*.
Figure 15: **PQ intervention for *P. vivax* in Pailin.** Lines represent annual medians for each individual year from 300 sampled model trajectories given the status quo and each radical cure scenario. Vertical dashed line is the December 2025 elimination target for *P. vivax.*
Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryAppendixReferencePDF.pdf