RESEARCH

Assessing a 2020–2025 primaquine intervention in Cambodia 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.

A number of data wrangling steps were conducted to produce the data the model was calibrated too. For example, some Provinces were combined to maintain static borders across the data period of 2011–2018. The population stratification for *P. vivax* incidence was provided as a proportion of cases by age and sex, from 2015–2019.

Therefore, data for each Province was pro-rated to achieve the correct proportion of cases for Males 15 years and older.

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,

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

if *P. vivax* is still present in 2025 in the model results, this additional intervention alone will not be sufficient.

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 results 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 modelled 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

Model calibration

For each of the 6 Provinces, calibrations such as that shown in Fig 1 for Pursat were conducted. The left column (A and C) represent the "General" population group, and the right column (B and D) the "Males 15 years and older" group. The top row (A and B) represent the "worst case" baseline incidence calibration, where the model is calibrated to the higher data values and is increasing trend after 2018. The bottom row (C and D) represent the "best case", where the model is calibrated to the lower values and has a decreasing trend. The other 5 Figures depicting the calibration are shown in Additional File **??**, Fig **??**–**??**.

Primaquine impact on burden of disease in Cambodia

The impact of Primaquine being provided to all Males 15 years and older from October 2020, will complete effectiveness, are shown for each Province and baseline incidence scenario in Figures 2–7. The "vivax infection" is an amalgamation of the exposed, uncomplicated, and severe malaria states, and "latent" refers to those with hypnozoites. The breakdown by state is shown in Additional file **??**, Figures **??**–**??**. Figures **??**–**??** show PQ provided to M15+ will have a substantial impact on transmission. However, elimination of *P. vivax* is not reached by 2025 for any of Provinces with the high and increasing baseline incidence, and is not reached even

for the low and decreasing baseline incidence for the Provinces with a higher current burden (Pursat).

Implications for surveillance

As the results showed in § , the PQ intervention will result in a lower prevalence of *P. vivax*. Therefore, the number of tests will change with time to have 99% confidence of detecting at least one case of *P. vivax* in males 15 years and older, in a given Province. Using the binomial approach, as outlined in § , we calculate the minimum target test number, assuming 100% sensitivity and specificity, with these numbers presented in Table 1. Note the prevalences used are based on the numbers shown at the time of the vertical dashed line in Figures 2–7. Most of the surveillance targets are within the current testing numbers of a Province **??**, however some are likely to be infeasible, such as the 89,418 for the low and decreasing baseline incidence scenario for Takeo, to detect at least one case in 2025.

Discussion

We have used a transmission model to explore the potential impact of Primaquine (PQ) for adult males, 15 years of age and older (M15+). We found PQ will be insufficient to reach elimination by the target date of 2025, for most of the Provinces and scenarios explored. This is an important piece of evidence to help guide the need for either further interventions or a change in target date for *P. vivax* elimination.

However, there are several limitations to this modelling study. Limitations include:

- Intervention scenario is beyond a "best case" as it is not possible to realise, due to limitations such as G6PDd prevalence in Cambodia, and a less than 100% effectiveness of PQ.
- Entirely a deterministic model, so the possibility of stochastic fadeout has been ignored. E.g. Fig **??** estimates < 2 cases by 2025.
- Actual background incidence is between the two scenarios posed, and we have not attempted to model the expected case. However, this approach enables us to answer the original question with confidence, that *P. vivax* is not likely to be eliminated by the target date of 2025 in Cambodia using PQ for Males 15 years and older in addition to current interventions.

The overly optimistic PQ scenario works in the opposite direction of the ignoring stochasticity.

We showed the earliest date this PQ intervention would eliminate *P. vivax* by, given this beyond best-case scenario. For more realistic elimination timeline estimates, we recommend using the latest surveillance data [**?**] to inform an expected incidence calibration, as well as the results of the current PQ trial underway in Pursat [**?**] to inform coverage, G6PDd prevalence, and PQ effectiveness estimates. This coupled with a a hybrid deterministic-stochastic approach, where the stochastic model is used once incidence becomes smaller, will help identify expected timelines with stochastic uncertainty estimates.

We identify surveillance test targets required to by 99% confident of detecting at least one case of *P. vivax* given the modelled annual incidence. This is to help inform minimum test targets to be sure of elimination. These numbers assume 100% sensitivity and specificity of *P. vivax* tests, hence are lower bounds on the deterministic model estimates.

We now have the Optimal malaria model (see, for example, [**?**]) for calibrated for *P. vivax* transmission for six Provinces in Cambodia, for two background incidences to account for changes in surveillance and interventions between 2011 and 2018. Since this uses the Optima model it is straightforward to explore other intervention scenarios, including optimal resource allocation [**?**].

Conclusions

We have used transmission modelling to answer a key question for Cambodia: if the use of Primaquine for males 15 years and older from October 2020, in addition to current interventions, will be sufficient to eliminate *Plasmodium 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 all Provinces by the target date. However, PQ is likely to have a substantial impact, on both blood stage infections (clinical and asymptomatic), and hypnozoite reservoirs. This is an important piece of evidence, to help guide the need for either further interventions or a change in target date.

List of abbreviations

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

CQ = Chloroquine

M15+= Males, 15 years of age and older

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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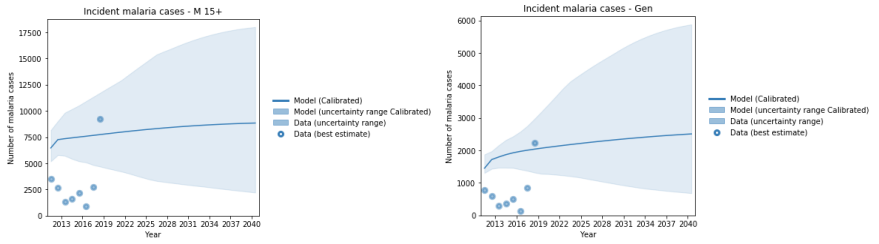
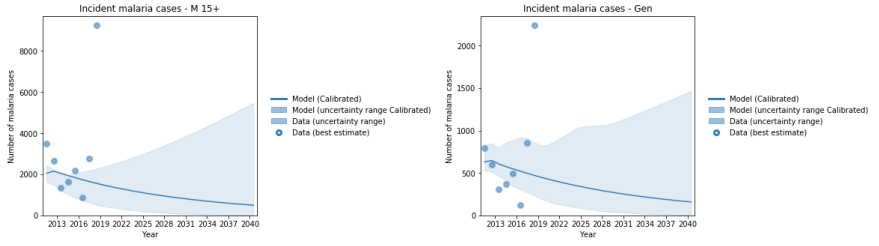


(a) M15+, high.

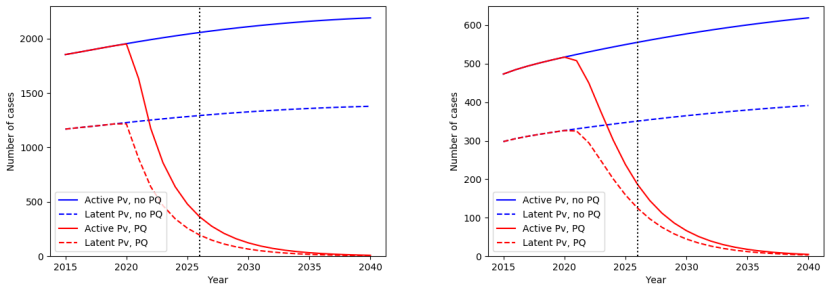
(b) Gen, high.



(c) M15+, low.

(d) Gen, low.

Figure 1: **Model calibration for Pursat.**



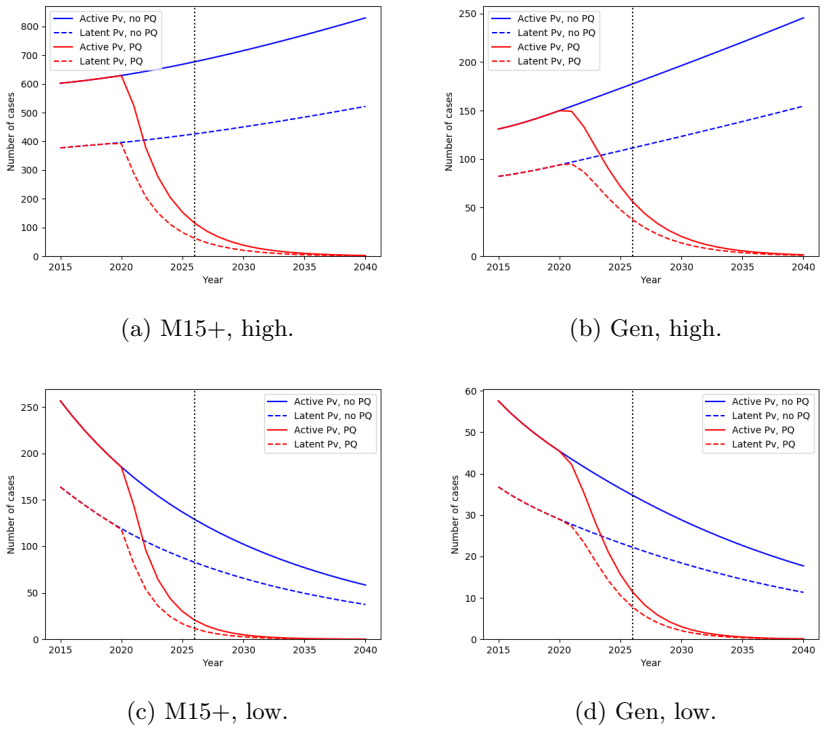
(a) M15+, high.

(b) Gen, high.

(c) M15+, low.

(d) Gen, low.

Figure 2: **PQ intervention for *P. vivax* in Pursat.** Vertical dashed line is the current elimination target for *P. vivax*.



(a) M15+, high.

(b) Gen, high.

(c) M15+, low.

(d) Gen, low.

Figure 3: **PQ intervention for *P. vivax* in Mondul Kiri.** Vertical dashed line is the current elimination target for *P. vivax*.

Tables

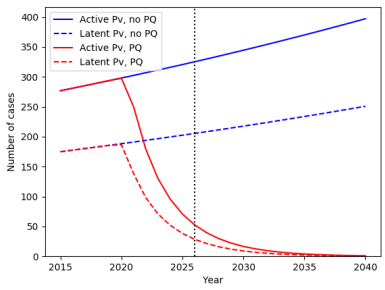
Table 1: Surveillance targets for 0.99 probability of detecting at least one case of *P. vivax* in a Province, given the scenarios outlined in § , assuming 100% sensitivity and specificity of the tests (so a lower bound on number of targets).

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

Additional Files

Additional file 1 — Model and data details

Detailed descriptions of the model and data are provided here, including supplementary figures with a further breakdown on the modelled impact.



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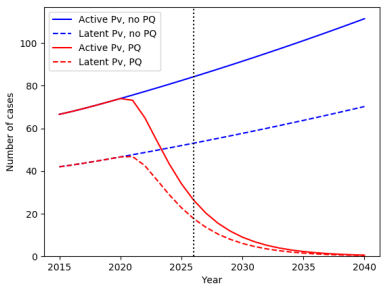

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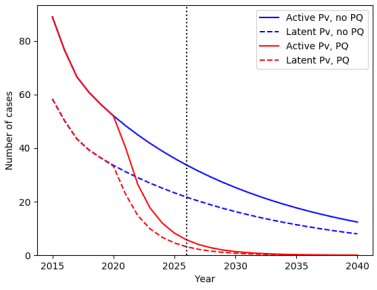

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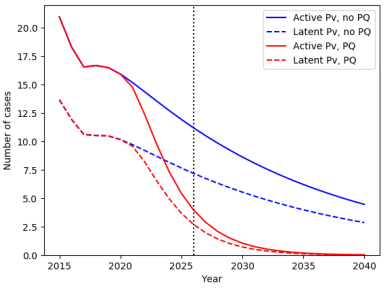
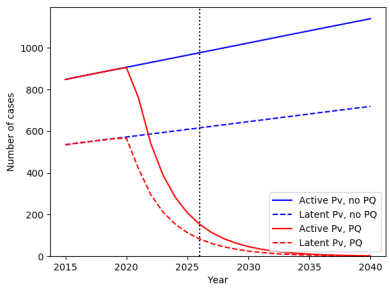


(d) Gen, low.

Figure 4: **PQ intervention for *P. vivax* in Kampong Chhnang.** Vertical dashed line is the current elimination target for *P. vivax*.



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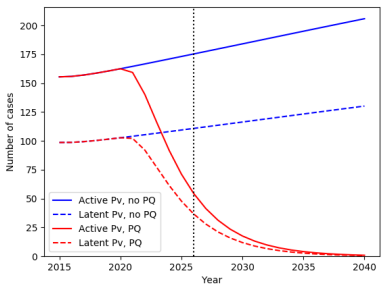

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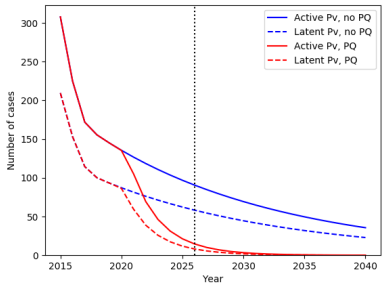

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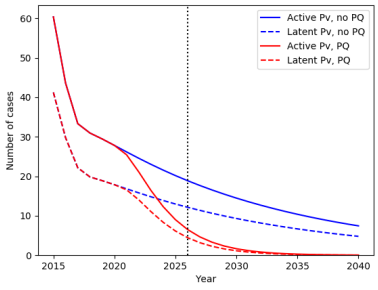
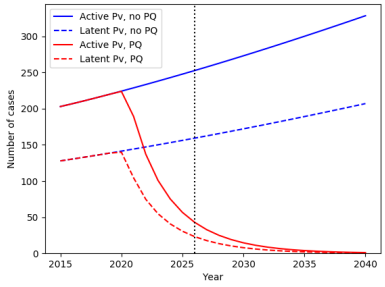


(d) Gen, low.

Figure 5: **PQ intervention for *P. vivax* in Battambang.** Vertical dashed line is the current elimination target for *P. vivax*.



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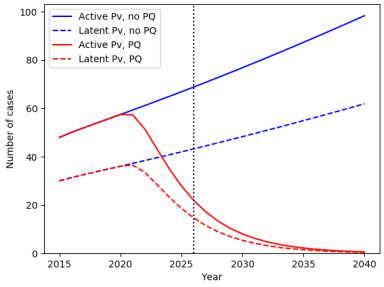

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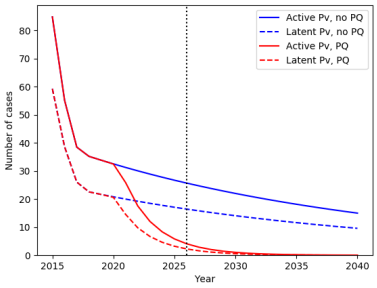

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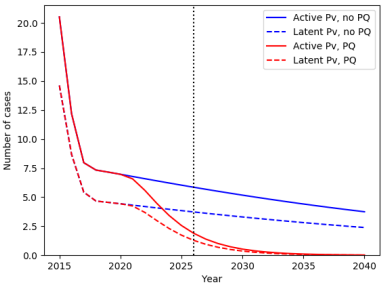
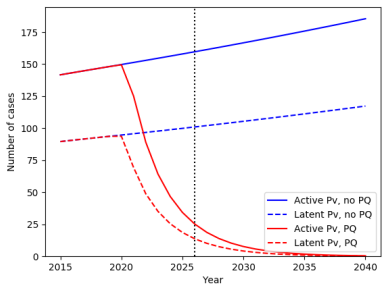


(d) Gen, low.

Figure 6: **PQ intervention for *P. vivax* in Pailin.** Vertical dashed line is the current elimination target for *P. vivax*.



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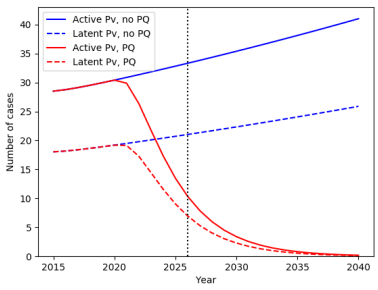

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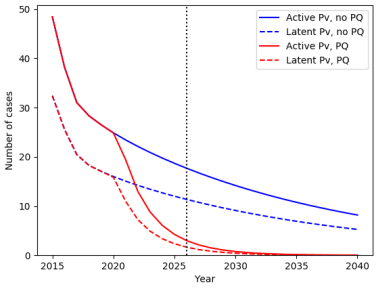

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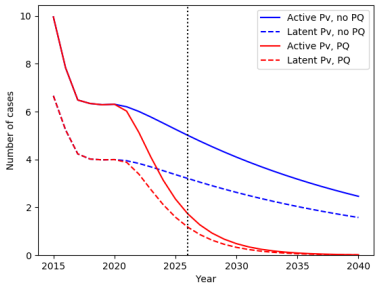

(d) Gen, low.

Figure 7: **PQ intervention for *P. vivax* in Takeo.** Vertical dashed line is the current elimination target for *P. vivax*.