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

Epidemic model

Programmatic response considered

Model calibration

Sensitivity analysis

Results

Current burden of disease in Cambodia

Model calibration and validation

Primaquine impact on burden of disease in Cambodia

Discussion

Conclusions

List of abbreviations

$P.\ vivax = Plasmodium\ vivax$

$\mathrm{PQ} = \mathrm{Primaquine}$

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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References

1. Koonin, E.V., Altschul, S.F., Bork, P.: Brca1 protein products: functional motifs. Nat Genet **13**, 266–267 (1996)
2. Kharitonov, S.A., Barnes, P.J.: Clinical Aspects of Exhaled Nitric Oxide. in press
3. Zvaifler, N.J., Burger, J.A., Marinova-Mutafchieva, L., Taylor, P., Maini, R.N.: Mesenchymal cells, stromal derived factor-1 and rheumatoid arthritis [abstract]. Arthritis Rheum **42**, 250 (1999)
4. Jones, X.: Zeolites and synthetic mechanisms. In: Smith, Y. (ed.) Proceedings of the First National Conference on Porous Sieves: 27-30 June 1996; Baltimore, pp. 16–27 (1996). Stoneham: Butterworth-Heinemann
5. Margulis, L.: Origin of Eukaryotic Cells. Yale University Press, New Haven (1970)

6. Orengo, C.A., Bray, J.E., Hubbard, T., LoConte, L., Sillitoe, I.: Analysis and assessment of ab initio three-dimensional prediction, secondary structure, and contacts prediction. Proteins **Suppl 3**, 149–170 (1999)
7. Schnepf, E.: From prey via endosymbiont to plastids: comparative studies in dinoflagellates. In: Lewin, R.A. (ed.) Origins of Plastids vol. 2, 2nd edn., pp. 53–76. Chapman and Hall, New York (1993)
8. Innovative Oncology
9. Smith, Y. (ed.): Proceedings of the First National Conference on Porous Sieves: 27-30 June 1996; Baltimore. Butterworth-Heinemann, Stoneham (1996)
10. Hunninghake, G.W., Gadek, J.E.: The alveloar macrophage. In: Harris, T.J.R. (ed.) Cultured Human Cells and Tissues, pp. 54–56. Academic Press, New York (1995). Stoner G (Series Editor): Methods and Perspectives in Cell Biology, vol 1
11. Advisory Committee on Genetic Modification: Annual Report. London (1999). Advisory Committee on Genetic Modification
12. Kohavi, R.: Wrappers for performance enhancement and obvious decision graphs. PhD thesis, Stanford University, Computer Science Department (1995)
13. The Mouse Tumor Biology Database. http://tumor.informatics.jax.org/cancer_links.html

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

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

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