










RESEARCH ARTICLE

REVISED **Malaria elimination transmission and costing in the Asia-Pacific: a multi-species dynamic transmission model**
[version 2; peer review: 1 approved, 1 approved with reservations, 2 not approved]

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Abstract







Background: The Asia-Pacific region has made significant progress in combatting malaria since 2000 and a regional goal for a malaria-free Asia Pacific by 2030 has been recognised at the highest levels. External financing has recently plateaued and with competing health risks, countries face the risk of withdrawal of funding as malaria is perceived as less of a threat. An investment case was developed to provide economic evidence to inform policy and increase sustainable financing.

Methods: A dynamic epidemiological-economic model was developed to project rates of decline to elimination by 2030 and determine the costs for elimination in the Asia-Pacific region. The compartmental model was used to capture the dynamics of *Plasmodium falciparum* and *Plasmodium vivax* malaria for the 22 countries in the region in a metapopulation framework. This paper presents the model development and epidemiological results of the simulation exercise.

Results: The model predicted that all 22 countries could achieve *Plasmodium falciparum* and *Plasmodium vivax* elimination by 2030, with

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the People's Democratic Republic of China, Sri Lanka and the Republic of Korea predicted to do so without scaling up current interventions. Elimination was predicted to be possible in Bangladesh, Bhutan, Malaysia, Nepal, Philippines, Timor-Leste and Vietnam through an increase in long-lasting insecticidal nets (and/or indoor residual spraying) and health system strengthening, and in the Democratic People's Republic of Korea, India and Thailand with the addition of innovations in drug therapy and vector control. Elimination was predicted to occur by 2030 in all other countries only through the addition of mass drug administration to scale-up and/or innovative activities.

Conclusions: This study predicts that it is possible to have a malaria-free region by 2030. When computed into benefits and costs, the investment case can be used to advocate for sustained financing to realise the goal of malaria elimination in Asia-Pacific by 2030.

Keywords

malaria, elimination, mathematical modelling, vivax, falciparum, Asia-Pacific




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gateway.



This article is included in the [Predicting the cost of malaria elimination in the Asia-Pacific collection](#).

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REVISED Amendments from Version 1

A section has been added on the impact of the model on policy development. The supplementary material has been updated with information on modelling of interventions and the Extended data repository has been reorganised. The DOI has been updated to reflect this.

With respect to drug combinations, while we acknowledge that candidate drugs for MDA may differ between countries, the intervention was modelled using the characteristics of DHA-Piperaquine. This detail has been added to the section describing MDA in the paper.

See referee reports

Introduction

Since 2000, considerable progress has been made in reducing the malaria burden in the Asia-Pacific. Both malaria cases and deaths have decreased by more than 50% between 2010 and 2015 in the 22 countries that constitute the Asia-Pacific region¹. Increases in political and financial commitment that enabled the scale-up of tools for preventing, diagnosing and treating malaria have contributed to achieving these gains. Many countries are now working towards national malaria elimination and a regional goal for a malaria-free Asia-Pacific by 2030 has received considerable political support².

Funding for malaria in the Asia-Pacific has increased significantly between 2000 and 2016 with the region accounting for 12–21% of global malaria funding between 2006–2010 from the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund). Funding has since plateaued and it is likely that it will be insufficient to support the resources required to achieve and maintain malaria elimination^{3,4}.

To this end, the objective of this study was to develop an investment case for malaria in the Asia-Pacific by estimating the costs and benefits of sustaining investments until elimination is achieved in the region. The investment case required the development of a mathematical model to project rates of decline to elimination by 2030 and determine the associated costs to achieve elimination in the Asia-Pacific region. As the Asia-Pacific region experiences both *Plasmodium falciparum* and *Plasmodium vivax* malaria, the mathematical model needed to incorporate the dynamics and control measures for both species. This modelling application would allow an analysis of various scenarios of malaria control and elimination interventions to determine the path to elimination in the region. Cost data would be incorporated into the epidemiological model to estimate the costs of elimination and the economic impact of interventions against the transmission of *Plasmodium falciparum* and *Plasmodium vivax* malaria.

Sri Lanka has been declared malaria-free by the World Health Organisation, while Afghanistan, Bangladesh, Bhutan, Cambodia, DPR Korea, India, Indonesia, Lao PDR, Malaysia, Myanmar, Nepal, Pakistan, Papua New Guinea, People's Republic of China, Philippines, Republic of Korea, Solomon Islands,

Thailand, Timor-Leste, Vanuatu and Viet Nam accounted for approximately 16 million cases of malaria and 33,000 deaths in 2016⁵. Between 2000 and 2016, WHO estimated malaria incidence in the WHO South East Asia Region (SEAR) and WHO Western Pacific Region (WPR) decreased by 48% and 12%, respectively, though the period 2014–2016 saw a rise in malaria incidence of 4% and 5% respectively while global trends remained relatively unchanged¹. In 2016 it was estimated that 8 550 000 (6 430 000, 11 140 000) *Plasmodium vivax* malaria cases occurred globally, and while that constituted only 4% of the global malaria burden, these cases accounted for 34% of all malaria cases in the SEAR and 23% of cases in the WPR. Furthermore, 75% of the global total *Plasmodium vivax* malaria cases occurred in India, Pakistan, Afghanistan and Indonesia¹. Given that the goal of malaria elimination applies to all malaria, elimination-focused interventions can serve to inhibit both *Plasmodium falciparum* and *Plasmodium vivax* malaria and with the high proportion of vivax cases in the Asia-Pacific, it is essential that any mathematical model aiming to predict the path to elimination in the region should be able to capture the dynamics of both species of malaria and the interactions between them⁶.

In the past, economic evaluations and costing of interventions against disease have commonly been conducted using decision trees or Markov models⁷. While these methods of analysis capture the direct outcomes of disease transmission (e.g. treated/averted cases), they do not capture the indirect transmission dynamics inherent in the biology of the disease (e.g. immunity and drug resistance). In the last decade, there has been a rise in the literature that incorporate the cost of interventions into dynamic transmission models to capture these indirect effects⁷. In their review, Drake *et al.* (2016) found 15 such modelling studies conducted between 2004 and 2014 that focused on malaria transmission and costing of interventions. The majority of these studies were focused on malaria in Africa, with no applications in the Asia-Pacific.

Dynamic models of malaria transmission have been used to simulate malaria transmission for over 100 years with a review of mathematical models for malaria available elsewhere⁸. Several dynamic models of *P. falciparum* malaria have been used to infer the prospects for elimination in an Asian-Pacific setting^{9–13} and since 2010, a number of dynamic models of *Plasmodium vivax* malaria transmission have been published^{14–18}. Recently published models of both *P. falciparum* and *P. vivax* malaria have employed dynamic mathematical methods^{19,20} and statistical techniques^{21–23}. To the knowledge of the authors, the model presented in this paper is the first dynamic multi-species (*P. falciparum* and *P. vivax*) model of malaria transmission incorporating both epidemiological and economic dynamics in a single framework.

The compartmental model developed to assess the potential of elimination in the investment case is a multi-species dynamic epidemiological-economic model that is applied in a metapopulation framework to capture the spatial heterogeneity in the Asia-Pacific. The spatial resolution of the model is at a

national level for each of the 22 countries, given the purpose to predict regional elimination and the availability of national data for all countries in the region. All models are simplifications of reality that are designed to describe and predict system behaviour. This paper presents the model development and epidemiological impact of the intervention simulation to predict the path to elimination in the region. The associated cost and economic benefits of achieving elimination are presented in Shretta *et al.*²⁴ and the computer application developed to showcase the project results, the METCAP application is presented in Celhay *et al.*²⁵.

Methods

Model generation

A dynamic compartmental model for *P. falciparum* malaria transmission was developed based on previously published models^{11,26–30}. The model was extended to include a companion model for *Plasmodium vivax* and incorporate interactions between the two species of malaria. The model framework is described in detail in Supplementary File 1, available as Extended Data³¹.

Key features of the *P. falciparum* model include four infection classes representing infections that are severe, clinical, asymptomatic and detectable by microscopy, and asymptomatic and undetectable by microscopy, with each infection class having an associated infectiousness based on infectivity data. The probability of individuals entering each class of infection is dependent on their immunity status. It is assumed that untreated individuals will transition from higher to lower severity infection classes as they recover and that they can be boosted to higher severity classes through superinfection. It is assumed that treated individuals test positive for histidine-rich protein 2 (HRP2) after clearance of asexual parasitaemia for different durations depending on the detection limit of the test used.

A companion compartmental model was developed for the transmission of *P. vivax* malaria. Its formulation is similar to the *P. falciparum* model with respect to the four infection classes, though there are key differences between the two model structures. *P. vivax* infections are characterized by relapses of malaria arising from persistent liver stages of the parasite (hypnozoites). It is assumed that infections may clear with the persistence of hypnozoites in the liver (dependent on a probability) and that these hypnozoites may trigger relapses of infection. The relationship between glucose-6-phosphate dehydrogenase deficiency (G6PDd) and *P. vivax* malaria is incorporated in the model through separate treatment regimens to account for G6PDd testing and radical cure. As with the *Plasmodium falciparum* model, it is assumed that untreated individuals will transition from higher to lower severity infection classes as they recover and that they can be boosted to higher severity classes on superinfection.

The *P. falciparum* and *P. vivax* models are independent models for the same population. The models are entangled together at each time step to incorporate interactions between the two species in the following manner:

1. Dual treatment (Treatment of a mixed infection)

The untreated population infected with *P. falciparum* malaria that are simultaneously infected with and being treated for *P. vivax* malaria with artemisinin-based combination therapy (ACT) or a drug that is effective against both species, will also be cured of their *P. falciparum* malaria. Likewise, ACT for a *P. falciparum* infection will also cure a *P. vivax* infection, though hypnozoites may be present after infection^{32,33}.

2. Triggering

It has been observed in many studies that clinical *P. falciparum* infections are often followed by *P. vivax* infection^{6,34,35}. It has been hypothesized that the subsequent appearance of *P. vivax* implies that a *P. falciparum* episode reactivates *P. vivax* hypnozoites³⁴. This is incorporated into the model with the population experiencing a clinical *P. falciparum* infection having a higher probability of *P. vivax* relapse compared to the rest of the population.

3. Masking

Different brands of rapid diagnostic tests (RDT) have different targets, and thus it may be the case that non-*falciparum* malaria is masked by *falciparum* malaria³⁶. A comparison of RDTs that are designed to differentiate *falciparum* malaria from non-*falciparum* malaria, but cannot differentiate between non-*falciparum* species nor identify non-*falciparum* malaria species within a mixed infection suggested that 11–22% of microscopy-confirmed non-*falciparum* cases are missed, with approximately 25% of these cases being declared as positive for *falciparum*. RDTs targeted to detect *P. vivax* specifically, whether alone or part of a mixed infection, were more accurate with tests missing less than 5% of *P. vivax* cases³⁶. To account for this it is assumed that 5% of *P. vivax* cases are treated as *P. falciparum* cases and will not be candidates for radical cure in the model.

A spatially explicit version of this multi-species model was applied to the 22 countries in the Asia-Pacific region. This enabled the estimation of the relative contribution of spatially targeted interventions in a spatially heterogeneous transmission setting. The region is divided into a number of interconnected patches with each patch representing a country having its own transmission intensity. The patches are connected spatially such that the risk of infection of an individual in a particular patch from an individual in another patch is negatively correlated with the distance between the patches.

The models were developed in R³⁷ and C++ and a full description of the mathematical model, the parameters driving the model and the model source code can be found on [GitHub](#) and [Zenodo](#)³¹.

Data

The data used to calibrate the model was obtained from several sources. The following annual data was extracted from the country profiles in the publicly available World Malaria Reports for the period 2000 to 2015^{1,3,37–44}:

1. Non-community cases (*P. falciparum* and *P. vivax*, separately)

2. Community cases (*P. falciparum* and *P. vivax* recorded jointly)
3. Number of ITN and LLIN sold or delivered
4. Number of people protected by IRS
5. Reported fatalities due to malaria
6. Population at risk (high, low transmission and active foci)
7. First-line treatment - (*P. falciparum* and *P. vivax*)
8. Year in which primaquine was adopted for the treatment of *P. vivax*
9. Type of RDT (years available)

This 15 year period was chosen to coincide with the timeframe of analysis for the investment case. Owing to differing reporting standards and interpretations of community cases, both community and non-community cases were grouped together. Additional data to inform the model calibration included the annual proportion of patients with malaria recorded in the national surveillance database in all 22 countries in the region and the estimates and ranges of the clinical burden of disease for both *P. falciparum* and *P. vivax* malaria from 2000 to 2015⁴⁵. This was used by Maude *et al.* 2019⁴⁵ to derive estimates and ranges of the clinical burden of disease for both *P. falciparum* and *P. vivax* malaria from 2000 to 2015 in the region. Where parameters driving the model could not be estimated from available data, they were sourced from existing literature. Details of the model calibration can be found in Supplementary file 1 in the Extended data³¹.

Results

Model Calibration and limitations

The model was calibrated to the estimated burden of disease separately for *Plasmodium falciparum* and *Plasmodium vivax* malaria and accumulated case fatalities. While reported distribution of LLINs and IRS were included in the model to inform changes in incidence, there was no data available on health system advances between 2000 and 2015, such as the introduction of community malaria workers etc. These were imputed based on observed changes in reported incidence. When this data becomes available, the model should be updated to include it.

This model has been validated with public data which typically has a low spatial and temporal resolution and is subject to a degree of uncertainty. It was not always possible to obtain historical intervention coverage data. Interventions have been modelled at a national level resulting in model predictions providing broad-stroke national guidance rather than a detailed sub-national strategy design. This is suitable to the purpose of the model which is to assess the path to elimination for the Asia-Pacific region through national intervention.

Modelling Interventions for malaria elimination

The mathematical model was developed to estimate the impact of intervention scenarios against the transmission of *P. falciparum*

and *P. vivax* malaria. Each scenario comprises several activities such as LLIN distribution and treatment as described below.

The scenarios were explored under two assumptions of future artemisinin and ACT partner drug resistance in *P. falciparum*: Stable Resistance, where the probability of treatment failure is constant at 5%, and Increasing Resistance, where the probability of treatment failure to artemisinin and the ACT partner drug is constant at 5% across all countries until 2018, then it increases steadily to 30% by 2025. These assumptions can be applied to countries individually or in relevant groupings. Mass Drug Administration (MDA) is an intervention that has received increasing interest in the last decade with respect to its role in malaria elimination^{13,28,29,46–50}. MDA is also incorporated in addition to any scenario in the following manner: five annual rounds of MDA at 50% coverage, from 2018, starting 4 months before the peak of the season using a drug with similar characteristics to dihydroartemisinin-piperaquine.

A detailed description of the scenarios modelled can be found in Figure 1. The scenarios are classified into four themes: Reverse (reducing current malaria activities), Continue (continuing malaria activities at current levels (2016) until 2030), Accelerate (scaling up activities and incorporating new interventions such as newly licensed drugs) and Innovate (assessing the impact of hypothetical interventions such as longer lasting more efficacious nets for example). Note that the IRS scenario is only considered in countries where an IRS programme was already established and functional. The use of primaquine as radical cure against *P. vivax* is incorporated in the baseline model commencing at the year of adoption outlined in the country profiles of the World Malaria Reports. The 'Single Dose New Pv Treatment' scenario therefore models the impact of switching from a 14-day primaquine regimen to a single dose regimen. Since the study, a candidate 'Single Dose New Pv Treatment' has been approved for use by the US Food and Drug Administration. The 'New Pf Drug' scenario described in Innovate theme is modelled as a candidate drug in response to the growing threat of artemisinin resistance.

Each of the 10 scenarios outlined in Figure 1 was simulated until 2030 under the assumptions of stable and increasing resistance and with the presence and absence of MDA as part of the national strategy. Given that the data used to validate the models did not distinguish between local and imported cases, malaria elimination could not be defined as zero local/indigenous cases. Using Sri Lanka's example of achieving elimination status in 2016, but reaching zero indigenous cases in October 2012⁵, the elimination threshold was defined as the incidence per 1000 population at risk that Sri Lanka reported to WHO in 2013, as this is a proxy for the level of imported cases one would expect to see in a country that has reached zero indigenous cases for the first time. This threshold was applied to the population at risk for all 22 countries.

The full set of simulation results has been made available on an online platform described in 25. The platform allows the user to

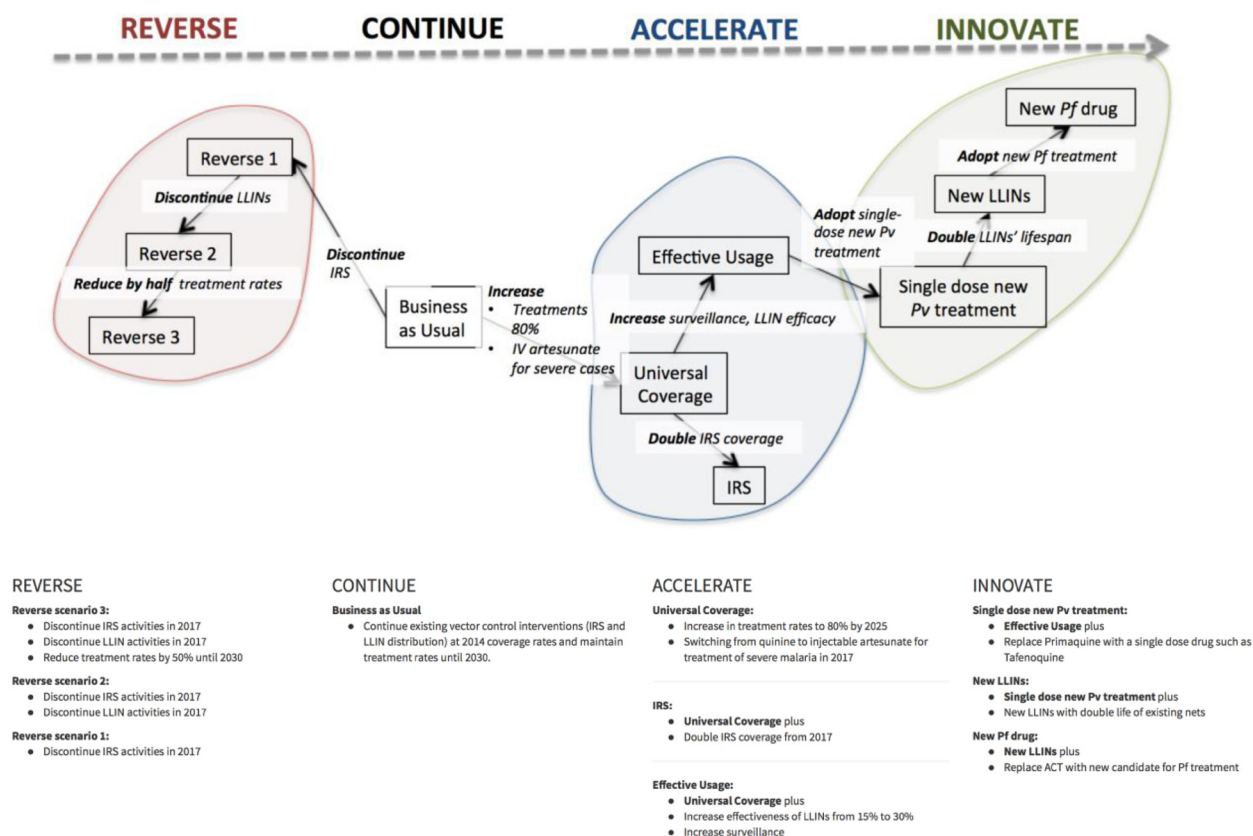


Figure 1. Description of scenarios modelled to assess if elimination could be achieved by 2030. The scenarios under the themes Continue, Accelerate and Innovate are nested (build on one another, reflected by underlining), while the Reverse theme contains scenarios to show the impact of reducing current activities against malaria transmission.

build integrated elimination strategies for groups of countries of interest using a selection of the scenarios. The full set of simulation results may be explored at www.metcapmodel.net and the key findings are presented in this paper.

Figure 2 shows that scaling up to achieve Universal coverage (as defined in the scenarios above) is not predicted to be sufficient to eliminate malaria by 2030 in the entire Asia-Pacific region. Elimination is predicted to be possible in countries such as the Philippines, Republic of Korea and Timor-Leste with Sri Lanka and the People's Democratic Republic of China being predicted to have achieved elimination by 2017 already. The ranges for disease burden estimates for the 22 countries that included accounting for completeness of reporting and access to healthcare was a major contributor to uncertainty in these estimates. The large range of uncertainty for some countries can be clearly seen in the wide interval of results. Figure 3 shows the range of years (minimum, median, maximum) in which elimination is predicted to be achieved under the Universal Coverage scenario. In line with Figure 2, countries such as Sri Lanka and People's Republic of China are predicted to reach elimination

by 2017, while the minimum and median year of elimination for Bhutan is predicted to be 2023 and 2029, respectively, the maximum year of elimination is recorded as "NO" to reflect that it occurs beyond 2030. This elimination timeline may be viewed for all ten scenarios under the assumptions of stable/increasing artemisinin resistance and with/without MDA.

The purpose of the study was to predict the set of interventions that would lead to malaria elimination by 2030. Figure 4 shows the minimum scenario to be deployed at a national level that is predicted to achieve elimination by 2030. A minimum scenario refers to minimum effort where, given the nested nature of the scenarios, Business As Usual < Universal Coverage < IRS < Effective Usage < Single Dose New Pv Treatment < New LLINs < New Pf Drug. All scenarios are considered 'less effort' without the addition of Mass Drug Administration. The selected minimum scenario is considered conservative as the full range of year of elimination (minimum, median and maximum) needs to be predicted to occur by 2030 under the assumption of increasing resistance over time. Where the range of elimination has not been predicted to be achieved by 2030 in any scenario,

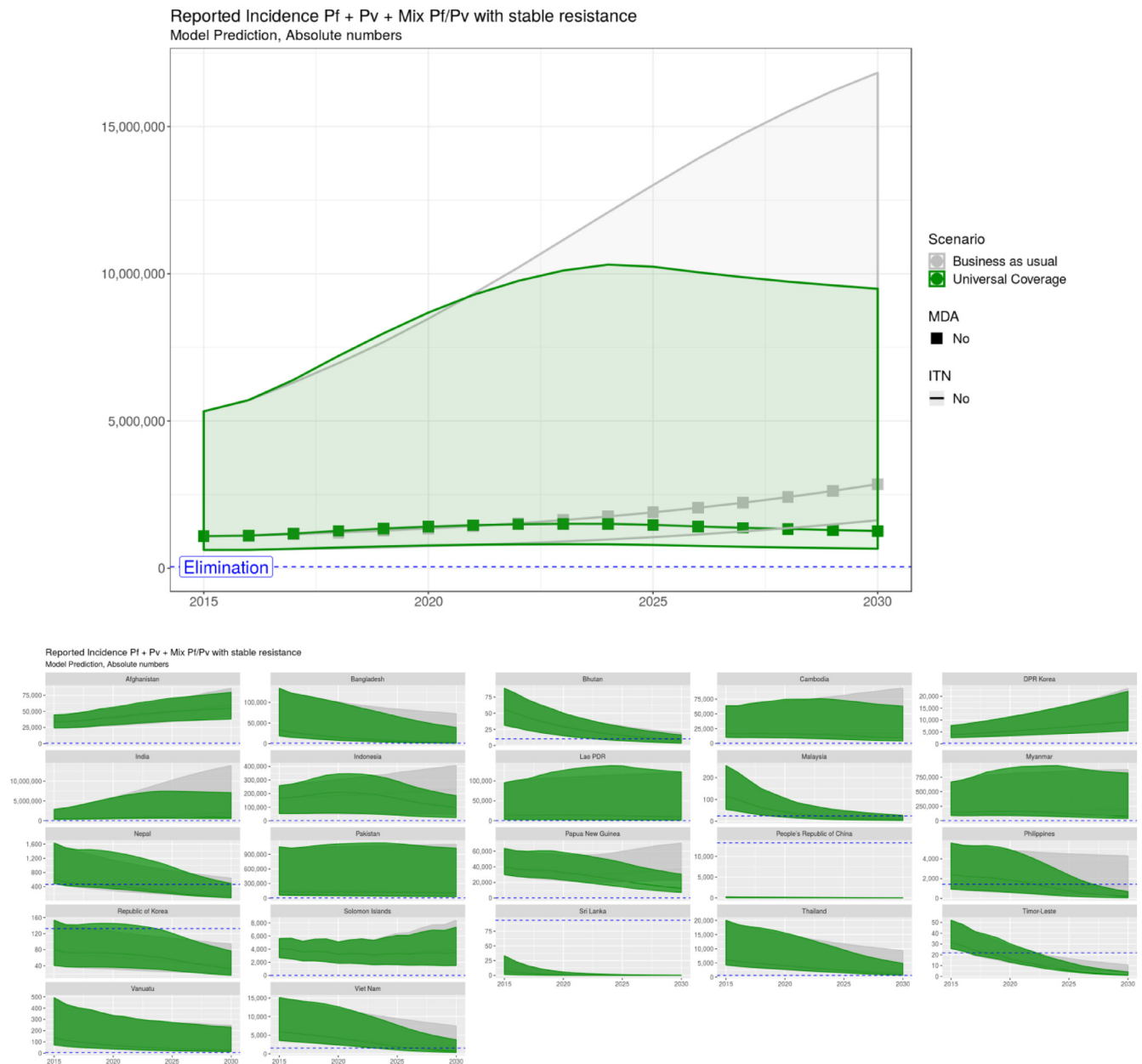


Figure 2. Predicted treated *P. falciparum*, *P. vivax* and mixed incidence under the Business as Usual scenario (grey) vs Universal Coverage scenario (green). Results are shown for the Asia-Pacific (above) and individual countries (below). Elimination threshold (blue dashed line).

a scale up in ITN coverage is added to the intervention mix, followed by MDA to assess the revised predicted range of year of elimination.

Table 1 compares the predicted year of elimination in the conservative intervention package with the national and regional goals for each of the 22 countries in the Asia-Pacific. The model predictions show that with the exception of Sri Lanka, People's

Republic of China, and Republic of Korea, all countries require a scale up in interventions to achieve malaria elimination. The impact of health system strengthening and achieving a higher rate of malaria infections being "tested and treated" is seen in the number of countries where the "Effective usage" scenario was predicted to be the minimum package required. The main results from the simulation study are presented in the 'Key findings' box.

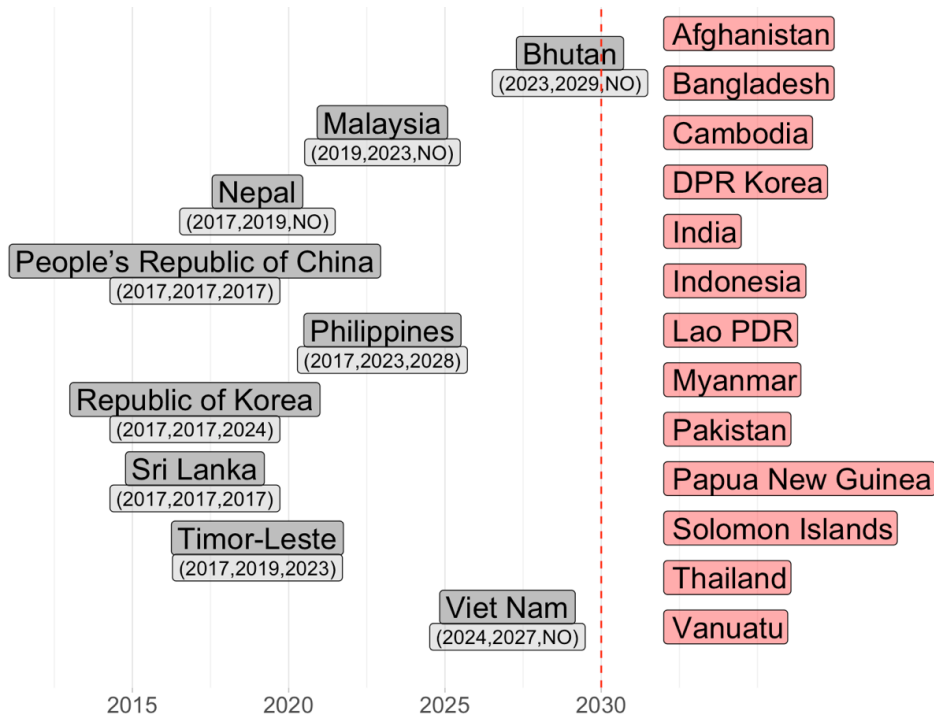


Figure 3. Predicted year (minimum, median, maximum) of achieving malaria elimination for both *P. falciparum* and *P. vivax* through the Universal Coverage scenario. Where the year is reflected as “NO”, malaria elimination was not predicted to be achieved by 2030. Country names are plotted at the median year of elimination and the length of the greyed out country name does not reflect the range of year of elimination. Countries are ordered alphabetically from top to bottom.

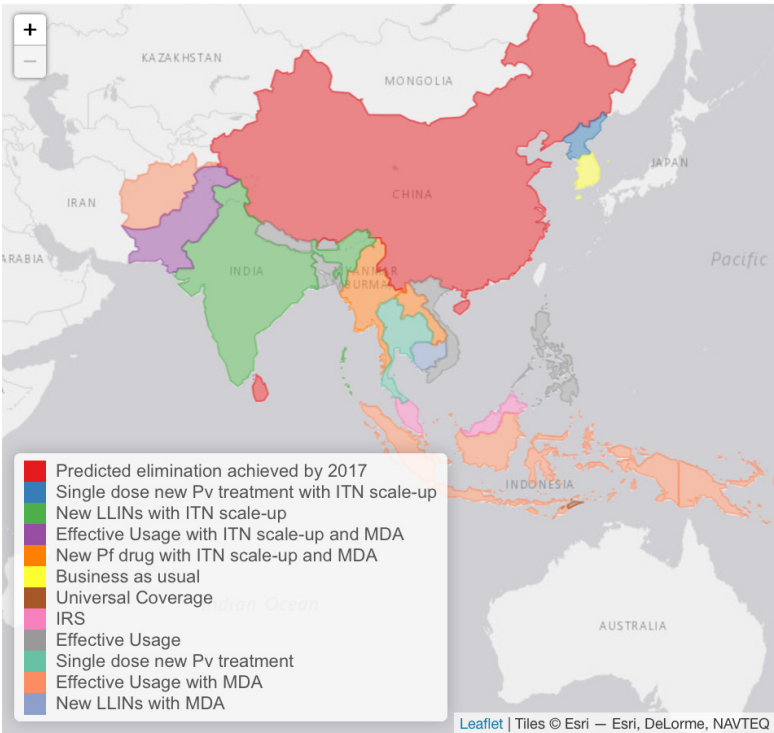


Figure 4. Predicted minimum package to achieve malaria elimination by 2030. A minimum package refers to minimum effort where, given the nested nature of the scenarios, Business As Usual < Universal Coverage < IRS < Effective Usage < Single Dose Radical Cure < New LLINs < New *Pf* Drug. All scenarios are considered ‘less effort’ without the addition of Mass Drug Administration.

Table 1. Minimum elimination package per country with national and regional goals for year of elimination.

Country	Minimal scenario for eliminaton	Range	National Goal	Regional Goal
Afghanistan	Effective Usage with MDA	2025 (2025,2027)		2030
Bangladesh	Effective Usage	2025 (2024,2029)	2025	
Bhutan	Effective Usage	2024 (2023, 2025)	2018	
Cambodia	New LLINs with MDA	2023 (2022,2030)	2025	2030
DPR Korea	Single dose new Pv treatment with ITN scale-up	2028 (2027, 2030)	2025	
India	New LLINs with ITN scale-up	2028 (2026,2030)		2030
Indonesia	Effective Usage with MDA	2025 (2022,2028)		2030
Lao PDR	New Pf drug with ITN scale-up and MDA	2025 (2022,>2030)		2030
Malaysia	IRS	2023 (2019,2029)	2020	2030
Myanmar	New Pf drug with ITN scale-up and MDA	2025 (2024,>2030)		2030
Nepal	Effective Usage	2022 (2017, 2026)	2026	
Pakistan	Effective Usage with ITN scale-up and MDA	2022 (2021,2030)		2030
Papua New Guinea	Effective Usage with MDA	2025 (2025,2028)		2030
People's Republic of China	Predicted elimination achieved by 2017		2020	2030
Philippines	Effective Usage	2021 (2017,2023)	2030	2030
Republic of Korea	Business as usual	2017 (2017,2019)	2017	2030
Solomon Islands	New LLINs with MDA	2028(2026,2029)		2030
Sri Lanka	Predicted elimination achieved by 2017		2012	
Thailand	Single dose new Pv treatment	2026 (2025, 2029)	2024	2030
Timor-Leste	Universal Coverage	2019 (2017,2024)		2030
Vanuatu	Effective Usage with MDA	2021 (2021, 2024)	2025	2030
Viet Nam	Effective Usage	2024 (2022, 2027)	2030	2030

Key findings from the METCAP model

- It is predicted to be possible for all 22 countries to achieve *Plasmodium falciparum* and *Plasmodium vivax* elimination by 2030
- The People's Democratic Republic of China, Sri Lanka and the Republic of Korea are the only countries predicted to achieve elimination without scaling up current interventions. Note that though Sri Lanka has already achieved zero indigenous cases, the definition of elimination employed by the model accounts for indigenous and imported cases, hence the continued prediction of a low level of (imported) cases since 2012.
- Elimination is predicted to be possible in Bangladesh, Bhutan, Malaysia, Nepal, Philippines, Timor-Leste and Vietnam through a scale up of LLINs (and/or IRS) and health system strengthening, suggesting that a "more of the same" approach is appropriate.

- When future innovations in drug therapy and vector control are simulated in addition to this scale-up, elimination is predicted to occur by 2030 in the Democratic People's Republic of Korea, India and Thailand.
- Elimination is predicted to occur by 2030 in all other countries only through the addition of MDA to scale-up and/or innovative activities. The analysis was limited to the consideration of MDA as a blanket intervention with other mass interventions (such as MSAT) not fully explored due to limitations on time, information and cost data.
- Future innovations in drugs, vaccines and vector control will also accelerate the path to elimination.

These findings are all predictions based on a mathematical model that is subject to a series of assumptions and informed by particular datasets.

Discussion

Leaders in the Asia-Pacific have committed to the regional goal of malaria elimination by 2030². The World Health Organization's 2017 *World Malaria Report* has shown that consistent progress is being made towards that goal with more than double the number of countries with less than 10,000 indigenous cases in the region in the last five years³. The Malaria Elimination Transmission and Costing in the Asia-Pacific study has developed a dynamic multi-species malaria transmission model to evaluate the impact of malaria interventions and their associated costs and benefits, to achieve elimination by 2030 in the Asia Pacific.

Asia-Pacific malaria is characterised by its diversity and range in terms of parasite species, malaria vectors, epidemiology and parasite resistance to drugs⁵¹. The region is dominated by *P. vivax* malaria, accounting for more than 75% of the global burden¹. The misconception of *P. vivax* malaria as benign has also contributed to it being neglected as a scientific, clinical, and public health issue⁵¹. The variation in malaria burden with *P. falciparum*-dominant countries (e.g. Bangladesh and Papua New Guinea) and *P. vivax*-dominant countries (e.g. Republic of Korea and Nepal) suggests that there will be variation in strategy for elimination. The range of packages predicted to lead to malaria elimination by 2030 shows that in some countries close to elimination, continuing in a 'business as usual' fashion will be sufficient, though the majority of countries will require a scale-up in malaria activities to progress towards elimination.

The METCAP model predicts elimination to be possible in Bangladesh, Bhutan, Malaysia, Nepal, Philippines, Timor-Leste, and Vietnam through a scale up of LLINs (and/or IRS) and health system strengthening. This speaks directly to the T3: Test, Treat, Track initiative by the World Health Organization where every suspected malaria case should be tested, every confirmed case should be treated with a quality-assured antimalarial medicine, and the disease should be tracked through a timely and accurate surveillance system⁵². The use of appropriate diagnostic tools is essential to the success of this strategy. While new RDTs that are highly sensitive to *P. vivax* malaria are available, the test formats in use are not always *P. vivax*-specific resulting in inappropriate management of *P. vivax* cases^{36,44,53}.

The ability to develop dormant liver stage parasites (hypnozoites) and the emergence of gametocytes before clinical symptoms makes *P. vivax* malaria prone to resurgence especially when control efforts cannot be sustained⁵⁴. Thus, it is critical that in order to reduce and eliminate *P. vivax* malaria, all developmental stages of the parasite in humans should be treated through radical cure. Radical cure is incorporated into the mathematical model through the adoption of a 14-day regimen of primaquine for all countries from the year of adoption specified in the World Malaria Reports. Though primaquine was adopted as policy in all countries, full-scale implementation is hampered by poor patient compliance with its 14-day treatment as well as the risk of severe haemolysis in individuals with deficiency of the enzyme glucose-6-phosphate dehydrogenase and the associated logistical and administrative burden of testing^{53,55}. Although all

22 countries have adopted primaquine to treat *P. vivax* in policy, it was not known which countries were successfully implementing the treatment. The model assumes that primaquine was used to treat *P. vivax* infections (with testing for G6PDd) from the year of adoption stated in the World Malaria Reports.

The mathematical model predicts elimination to occur by 2030 in Afghanistan, Cambodia, Indonesia, Lao PDR, Myanmar, Pakistan, Papua New Guinea, Solomon Islands and Vanuatu only when MDA is added to the scale-up of other interventions such as LLINs and IRS and/or future innovations. MDA is a costly intervention resulting in a temporary reduction in transmission, and in the absence of scale-up of other interventions, such as vector control, mathematical models have predicted that transmission would return to pre-administration levels^{26,29,48}. The analysis was limited to the consideration of MDA as a blanket intervention with other mass interventions (such as MSAT) not fully explored due to limitations on time, information and cost data. It is expected that in reality, targeted or focal interventions will be deployed as countries move towards elimination. By reducing the expected population at risk and assuming a relatively low coverage of MDA, the model can simulate targeting of MDA in a simplistic way, but ideally this and other focal interventions would be simulated using an individual-based model based on detailed sub-national data and in close collaboration with NMCP partners.

The minimum elimination scenarios proposed in the METCAP model were simulated under the assumption of increasing treatment failure as a proxy for growing ACT resistance. For simplicity, this was simulated as being the same across all 22 countries in the minimum scenarios only. While the predictions can be considered to be conservative in light of this assumption, it highlights the need for increased surveillance and resistance monitoring to stem the emergence and spread of resistance throughout the region. Increasing efforts towards prevention, diagnosis and treatment and strengthened surveillance in the Greater Mekong Sub-region could push the region into elimination, simultaneously solving the problem of artemisinin resistance.

Equally important to effective National Malaria Control/Elimination Programmes are strong sub-national programmes and evidence-based strategies, founded upon sub-national surveillance and response⁵⁶. With countries in the Asia-Pacific region characterized by large mobile and migrant populations, heterogeneity in vector species and parasite distribution, and differences in climate and terrain, the distribution of malaria within countries is very diverse. A limitation of the METCAP study is the national resolution of the mathematical model. Such a focus was necessary due to the availability of publicly available annual national data in the World Malaria Reports. The scope and duration of the project was such that it was not possible to negotiate data sharing agreements for sub-national data for all 22 countries in the region. As such a choice was made to sacrifice depth for breadth in order to answer the research question. Thus, the purpose of the METCAP model is to make broad-stroke predictions for the region capturing only national characteristics of the constituent countries with the goal of predicting the

approximate costs of elimination. The model should not be used in its current form to inform national or sub-national strategies. All models are simplifications of reality that are designed to describe and predict system behaviour and are justified by the assumptions on and data with which they are developed. Subsequent extensions of the METCAP model include incorporating sub-national data for Cambodia and Lao PDR to inform sub-national policy and assess the prospects for sub-national elimination.

The METCAP model and application has already been valuable to countries in the Asia Pacific in predicting and visualizing the effect of various interventions on the transmission curve. The model has also allowed the development of robust investment cases for political commitment and financial resources for malaria elimination. For example, application of the METCAP model and the subsequently developed investment case enabled Bangladesh to commit to malaria elimination, launching its new malaria elimination plan (2017–2020) and reconfiguring their programme. Government financing has increased to support strengthened elimination strategies. Similarly, the application of METCAP in Indonesia facilitated the malaria programme to strengthen their surveillance systems by introducing case foci and investigation in support of malaria elimination.

Conclusion

The misperception of malaria in the Asia-Pacific region as a less severe but essentially similar problem to African malaria can lead one into the mechanical application of the same tools and strategies⁵¹. Eliminating malaria from the Asia-Pacific region requires specific technical strategies and tools for coping with all of its unique features. In the current climate of decreasing global malaria funding, countries with a lower malaria burden are becoming a lesser priority for donors. The METCAP study has predicted that it is possible to achieve both *P. falciparum* and *P. vivax* elimination in the Asia-Pacific and sustained financing needs to be secured to realise this goal of malaria elimination by 2030.

Data availability

Underlying data

The data used to calibrate the model was obtained from the country profiles and annexures of the publicly available World Malaria Reports for the period 2000 to 2015^{1,3,37–44}. The set of

annual reports from 2008 onwards can be accessed at http://www.who.int/malaria/publications/world_malaria_report/en/. All other data was sourced from published literature.

Extended data

Supplementary file 1. Description of the methodology, equations and parameters underlying the mathematical model for *P. falciparum* and *P. vivax* malaria transmission. DOI: <https://doi.org/10.5281/zenodo.3346651>³¹.

Data are available under a [CC0 1.0 Universal license](#).

Software availability

Model source code available from: <https://github.com/sheetalsil/METCAP>

Archived source code at time of publication: <https://doi.org/10.5281/zenodo.3346651>³¹.

License: MIT Licence.

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Gerhart Knerer

University of Southampton, Southampton, UK

Christine Currie 

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The comments below have been produced by myself (Christine Currie) and Gerhart Knerer.

This is an impressive paper with a huge amount of work behind it in setting parameter values and validating the methodology. The authors have used a number of different data sources for validation and this gives some confidence in their results.

A few things remained a little unclear after reading through the article that we would appreciate some clarification on.

1. The title of the paper is 'Malaria elimination transmission and costing in the Asia-Pacific' but the paper itself does not appear to include any costings, nor are these listed in the supplementary material. While it is possible to see how costs could be included, we were anticipating seeing cost estimates based on the dynamic model but these have not been included. This makes it difficult to see what the investment case is for the suggested interventions.
2. Several different terms are used to describe how the spatial interactions work within the model. In the main paper (Page 4, paragraph beginning "A spatially explicit version ..") interactions are described as taking place between "patches", which seem to be synonymous with countries. If so, is there a reason to add the additional term "patches" rather than just using "countries" throughout? The supplementary material suggests that interactions are between villages (bottom of page 1, supplementary material). I believe this is a wording issue rather than a modelling issue. Further to this, it would also be useful to clarify what is meant by "individuals" on Page 4 of the main paper when discussing the spatial effects - are these just people or does the effect also apply to vectors?
3. **Sensitivity Analyses:** it is useful to see estimates of uncertainty or confidence in the

predictions. On page 9, the authors state that '.....These findings are all predictions based on a mathematical model that is subject to a series of assumptions and informed by particular datasets.' However, there is no indication of how the results will change if the assumptions are changed. Apart from model structure uncertainty, parameter uncertainty could potentially be very significant. When considering uncertainty and model result sensitivities, it is useful to understand where the greatest contribution to uncertainty originates. Have the authors carried out a sensitivity analysis that we have missed?

4. There are a lot of acronyms used in the article and it would be good if these could be defined on first use. Most are, but I spotted at least one (IRS) that wasn't.
5. The current analysis considers a set of scenarios for treatment in priority order and tests these with or without Mass Drug Administration (MDA). I think it would be useful to indicate which countries in the region have used MDA strategies in the past for readers less familiar with the malaria world.
6. Figures 3 and 4 in the Supplementary Material show that the model fits data from some countries relatively poorly. These look to be countries where the number of data points is relatively small but it would still be useful for the authors to attempt to explain this for countries where the trend and numbers look very different from the data and also include some acknowledgment of this in the main paper.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: My main area of research is in mathematical modelling. I am not an expert on malaria and so am unable to comment on these areas of the article.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have

significant reservations, as outlined above.

Reviewer Report 28 February 2020

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Emma S. McBryde 

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I have agreed to provide a review of the paper, and have disclosed that I am an infectious diseases physician, mathematical modeler and biostatistician, but not a malaria modeler. I understand the structure of the malaria transmission model, but cannot comment about choice of parameters, particularly those for interventions, beyond whether they have been justified adequately in the text.

I also disclose that I have a PhD student in common with the senior author of the paper and we plan to co-publish material in the near future.

My major review comments:

Reviewer 1 may have missed some elements of the article when providing their report, such as the absence of detail regarding the model. The criticism that the paper does not provide details of the model or reference peer review publication are incorrect.

Reviewer 2 makes a number of general criticisms including

- The study has sacrificed breadth for depth: in particular noting that:
 1. The model is compartmental with sub-compartments being 22 countries in the Asia Pacific –no subnational detail is used
 2. Subcategories for age/heterogeneity of exposure is absent.

The authors respond by suggesting that there are two schools of thought with regards to modelling, one being to provide broad overview of circumstances to assist policy makers in a rapid time scale, the other being to provide detailed models closely linked to datasets to provide local information.

My opinion is that both types of modelling philosophies are valid and the journal should accept either provided they will be of interest to readers and are adequately justified with assumptions made clear.

On this note, the authors have included a clear explanation of the model, the data sources and the assumptions.

It would be wise for the authors to add a few (more) caveats to the discussion such as...“as this

model did not incorporate subnational data, exposure heterogeneity or age stratification, it could not provide predictions for interventions targeting subpopulations”.

- The study does not distinguish between currently available interventions and those yet to be developed or tested

My reading is that the authors did draw this distinction clearly in Figure 1, however time has passed and now one of the innovations has become reality.

The authors should provide more detail about mass drug administration and Pv treatment including assumptions about cascade of care –after a country commences Pv radical cure, do the authors assume all patients (other than the 5% missed and those with G61PDdef) with Pv get primaquine? What is the assumed MDA coverage and effect?

Comments regarding parasite biology:

Reviewer 2 comments that an assumption is made to parasite biology which is only backed up by old references. The authors respond by providing newer references which provide similar values. My view of this is that assumptions need to be made when modelling based on available literature, even if this literature is uncertain. It would be valuable to assess whether the model results are sensitive to any of the parameters that have a high level of uncertainty, and to incorporate this uncertainty into results. If this is not done then there needs to be full disclosure of this in the manuscript and the potential for the results to be sensitive to assumptions.

Regarding the comment about parasitic sterilizing immunity, the reviewer has acknowledged this was a misinterpretation, as partial immunity is incorporated into the model.

Timing comment: the reviewer suggests that the time of intervention should be updated to the current year (or 2018, the most recent published results, containing data to 2017). Authors respond that the work carried out was around a specific funding cycle and questions related to this. Interventions commence in 2017, submission of the paper was in early 2019. I think this is a reasonable delay between the commencement of model simulation time (2017) and the time that the paper was submitted for publication, given the work is likely to have been carried out to inform policy makers prior to publication. In addition, the general nature of the conclusions and the time scale of the model do not require revision based on one additional year of reporting. Furthermore, the delay in the peer review of the paper is now contributing to this gap.

Model calibration

Reviewer 2 is concerned that the outputs of the model may have been calibrated with reported cases rather than an estimate of inferred actual cases. Authors respond that this is not the case and indeed they used estimated results as suggested by the reviewer, and this is clear in the manuscript.

Final comment:

Many of the criticisms of reviewer 1 and reviewer 2 arise from not finding the information that they seek. Some (but not all) of the answers to their concerns are found in the supplementary material. I therefore suggest the authors consider bringing some of the supplementary material into the manuscript, subject to the editorial rules.

I think that the paper is already quite detailed and an alternative may be to make the supplementary material more accessible. I had to clone into Github, and I think the only other

alternative offered was a zip file. Can the SOM be provided in the form of figure files or similar to help readers who want to delve further to access it easily?

My minor review comments:

1. There are many instances of abbreviations used without first defining these terms ITN, LLIN for example. Please ensure these, and others, are defined on first use.
2. In paragraph 4 of results, you describe Sri Lanka as being used as an example of a country with elimination of endogenous transmission but continuing to have imported cases. It is unclear to me how the Sri Lanka data are used in general in the model. Do you use travel data to make assumptions as to how the same effect may occur in other countries, and does this effect reduce over time as the region in general gets closer to elimination? More detailed explanation of assumptions is required here.
3. In results section paragraph starting Figure 2; the sentence starting "The ranges for disease burden..." should be reworded for clarity and ease on the reader. At first, I took "estimates" to be a verb and later realized the sentence starts to make sense if it is a noun.
4. Figure 2 is an important result – in fact the most important result in the paper. I suggest improving the colour coding. It is clear from text and the figure caption that there is a graded result moving from business as usual up through universal coverage etc. However, the interventions below predicted elimination achieved by 2017 are not as clear in terms of being part of a sliding scale. Can I suggest that you provide a heat map style of colour coding (shades of yellows, orange and red for example) and provide additional interpretation of where all of the different interventions fit into the scale.
5. Top of page 11 "The model should not be used in its current form to inform national or sub-national strategies."
I suggest changing this a little, as the purpose of the study is surely to provide some information to the region. Suggest something like: The model is not designed to provide detailed information to countries for direct decision support at a national or subnational level.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: As mentioned, I know Prof Lisa White, senior author of the manuscript, and she is a co-advisor for one of my PhD students. We have not yet co-published together but are likely to do so in the near future.

Reviewer Expertise: Infectious diseases modelling.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 24 September 2019

<https://doi.org/10.21956/wellcomeopenres.16764.r36174>

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Michael T. White 

Institut Pasteur, Department of Parasites and Insect Vectors, Paris, France

I appreciate the authors' considered response to my comments, and respect their approach to the problem at hand. As mentioned by the author, there certainly are differences in philosophies in relation to depth versus breadth for mathematical models and their application to public health policy. And this is okay.

In the more traditional peer review process, it would be left to a disinterested external party (the academic editor) to weigh these differences in value judgement, and if this person were to disagree with my opinion, that would be fine, as I'm very often wrong about these sorts of things. I'm unfamiliar with this more innovative and transparent process, and am genuinely uncertain about the optimal way forward. I stand by my original assessment, whilst also acknowledging the reasonable position taken by the authors. For these reasons, I will be stepping back from the peer review process for this article.

Mathematical model

I completely agree that both differential equation based and individual based models are useful and appropriate tools for infectious disease modelling. In this case, differential equation models are appropriate, albeit with the limitation that it's challenging to formally model elimination.

Transmission units

Selecting an ideal unit for modelling a transmission system is always challenging. In my opinion, entire countries, especially ones as diverse as Indonesia, are a bit on the large side.

Parasite biology

The clarification on sterile immunity is welcome. In fact, the misunderstanding arose from my incorrect reading of the differential equations.

Time scale

I'm still of the opinion that it's best to use the most up to date data possible.

Intervention models & Supplementary file

The inclusion of descriptions of the intervention models in the supplementary file is a welcome addition.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Mathematical modelling of *P. vivax* and *P. falciparum* transmission; Malaria epidemiology; Serology; Cost-effectiveness analysis; Statistics.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 24 Nov 2019

Sheetal Silal, University of Cape Town, Rondebosch, South Africa

The response has been drafted by Dr Sheetal Silal and Professor Lisa White.

Many thanks for the response. We invite robust constructive criticism always and hope to continue challenging and being challenged by our respected colleagues. Regarding the comment on more recent data, we would like to inform the reviewer that a follow-up study is under way to update the model for four countries in the region.

As the reviewer has concluded that they are “genuinely uncertain about the optimal way forward” and expressed the desire to step back from the peer review process, we did also wish to step away but have discovered that, once submitted, the paper can never be withdrawn even if repeatedly rejected. Our research is now in a potentially perpetual state of published but rejected, given the influence that two rejections may have on future reviews.

We sympathise with the reviewer’s surprise that there is no editorial input, except that in our case the editor did intervene to request we adjust one of our responses for tone, although refuses to intervene with reviews which are inaccurate or incomplete.

When we brought these issues up with the editorial team, each statement (ours or the reviewers) had the response of either:

A. Everyone may have their own opinion regardless of the accuracy of their statements.

B. All material may be edited at the discretion of the editors to ensure constructive discussion.

In addition we were reminded that:

C. We may not withdraw our article and it cannot be published elsewhere.

Competing Interests: None

Version 1

Reviewer Report 14 May 2019

<https://doi.org/10.21956/wellcomeopenres.16097.r35197>

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Andrew P. Morse 

¹ Health Protection Research Unit in Emerging and Zoonotic Infections, National Institute for Health Research (NIHR), Liverpool, UK

² School of Environmental Sciences, University of Liverpool, Liverpool, UK

This is a very policy push type of paper.

Unfortunately there has been no explanation of the model that has been used. As far as I can see the model is unpublished and has not undergone any peer review. The only reference given is to a code repository.

It is also not made clear if the model is a development of earlier work and certainly there are apparently no citations to make these types of links.

I hope this is an unfortunate oversight by the authors and that it can be rectified. Until this is the case, this paper should not be used for the way it is intended.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Climate driven numerical vector borne disease modelling, applications of ensemble prediction systems for seasonal forecasts and climate projections.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 21 Nov 2019

Sheetal Silal, University of Cape Town, Rondebosch, South Africa

This response has been resubmitted under the name of the lead author, as it was previously under the name of the submitting author. The response has been drafted by Dr Sheetal Silal and Professor Lisa White. Comments in italics are by the authors while regular text are excerpts from the reviewer's report.

It is unfortunate that this reviewer was not aware of the full set of equations provided in the supplementary files. His assertion that the model structure was not clearly defined and his decision to reject the manuscript may have been influenced by this issue. We have made further efforts to direct readers to the model equations in the revised manuscript beyond the statements provided in the original main text.

This is a very policy push type of paper.

The authors make no apologies for using mathematical modelling to support policy development. This is a valid activity for econ-epi modellers and some would argue a responsibility to contribute to global health emergencies where there is a call to arms for the entire research community to help. Mathematical modelling has been used to influence health policy for over 50 years with several organisations highlighting the contribution it can make to the goal of malaria elimination^{1,2}. Similarly during the 2014 Ebola crisis in West Africa, the World Health Organisation called out to the entire research community, modellers included, to answer key operational questions³.

- 1. Global Partnership to Roll Back Malaria, Chitnis, Nakul, Schpira, Allan, Smith, David, Hay, Simon I. et al. (2010). Mathematical modelling to support malaria control and elimination / Nakul Chitnis ... [et al]. World Health Organization.*
- 2. The malERA Consultative Group on Modeling (2011) A Research Agenda for Malaria Eradication: Modeling. PLoS Med 8(1): e1000403.
<https://doi.org/10.1371/journal.pmed.1000403>*
- 3. World Health Organisation (2014) Statement on the 2nd meeting of the IHR Emergency Committee regarding the 2014 Ebola outbreak in West Africa. Accessed: 24/05/2019.
<https://www.who.int/mediacentre/news/statements/2014/ebola-2nd-ihr-meeting/en/>*

Unfortunately there has been no explanation of the model that has been used. As far as I can see the model is unpublished and has not undergone any peer review. The only reference given is to a code repository. It is also not made clear if the model is a development of earlier work and certainly there are apparently no citations to make these types of links.

The Extended Data section at the end of the manuscript states "Supplementary file 1. Description of the methodology, equations and parameters underlying the mathematical model for P. falciparum and P. vivax malaria transmission. DOI: <https://doi.org/10.5281/zenodo.257547431>. "

This leads to a folder containing a few files, one of which is named "Supplementary file 1.pdf". This pdf document contains the description of the underlying mathematical model. The Methods section paragraph one also refers to this material as "The model framework is described in detail in Supplementary File 1, available as Extended Data³¹. Reference 31 takes one to same folder.

Additionally the first paragraph states "A dynamic compartmental model for P. falciparum malaria transmission was developed based on previously published models^{11,26–30}. The model was extended..." These references are to publications with models developed by the authors (along with co-authors of those papers).

In order to make the Supplementary file easier to locate within the referenced repository, the model code has been placed in a sub-folder.

I hope this is an unfortunate oversight by the authors and that it can be rectified. Until this is the case, this paper should not be used for the way it is intended.

It is an unfortunate oversight of the reviewer in this case. The METCAP model and application has already been valuable to countries in the Asia Pacific in predicting and visualizing the effect of various interventions on the transmission curve. The model has also allowed the development of robust investment cases for political commitment and financial resources for malaria elimination. For example, application of the METCAP model and the subsequently developed investment case

enabled Bangladesh to commit to malaria elimination, launching its new malaria elimination plan (2017-2020) and reconfiguring their programme. Government financing has increased to support strengthened elimination strategies. Similarly, the application of METCAP in Indonesia facilitated the malaria programme to strengthen their surveillance systems by introducing case foci and investigation in support of malaria elimination.

Competing Interests: None

Reviewer Report 13 May 2019

<https://doi.org/10.21956/wellcomeopenres.16097.r35383>

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Michael T. White 

Institut Pasteur, Department of Parasites and Insect Vectors, Paris, France

This article attempts an extremely ambitious goal of developing and applying mathematical models of *P. falciparum* and *P. vivax* transmission (and their interactions) to 22 countries in the Asia-Pacific, and simulating the potential impact of a wide range of malaria control interventions. In casting the net so wide, I fear the authors have sacrificed depth so that it's hard to be confident in specific predictions.

I certainly see the value for making the case for malaria elimination activities in the Asia-Pacific, and the need for advocacy in this space, but great care must be taken to distinguish between which scenarios are based on the reality of up to date data and currently available interventions, and which scenarios are based on interventions that have yet to be developed (e.g. new *Pf* drug and new LLINs), or yet to be tested at national scale (e.g. repeated rounds of MDA).

Mathematical model

The authors describe a compartmental differential equation model. Notably this does not have an individual-based structure, or incorporate age or heterogeneity in exposure to mosquito bites.

Transmission units

The key transmission units being modelled appear to be 22 countries in the Asia-Pacific. Within each country, transmission is enormously heterogeneous. For example, in Indonesia 141 million people live on the island of Java where there is little or no transmission, and 3.5 million live in Papua where there is intense transmission. Another key issue relates to the denominator population being modelled. For example, in China is it all 1.4 billion people, or just those who live in at risk areas? If those in at risk areas, how does this change over time?

Parasite biology

Within the *P. vivax* research community, the evidence base for the duration of asymptomatic

blood-stage infections is surprisingly weak. The authors assume a value of 130 days citing two old textbooks which I was unfortunately able to access easily^{1,2}.

In both the *P. falciparum* and *P. vivax* models, the duration of immunity in an individual without challenge is $1/\omega = 1$ year. The equations suggest this is sterile immunity, which doesn't agree with much of what is known of *Plasmodium* infection biology. This issue is likely to be particular important for *P. vivax* when relapses are accounted for.

Time scale

The time scales for simulation seem a little out of date. The model is calibrated to data from 2010 – 2015, with simulations provided from 2015 – 2030, and changes in interventions occurring in 2017. It's now midway through 2019. The 2018 World Malaria Report was published in November 2018, containing data up as far as 2017.

Drug treatment

The drug combinations used for MDA are not specified. Many countries in the Asia-Pacific have *P. vivax* radical cure with primaquine in their national treatment guidelines, but few routinely administer it due to the absence of easily available testing for G6PD deficiency. The incorporation of G6PD deficiency in the *P. vivax* transmission model is unclear: it appears to only be accounted for after treatment is administered.

The 'Single Dose New Pv Treatment' that is referenced is presumably tafenoquine which was licensed by the US FDA in July 2018.

Intervention models

No details of how intervention models were implemented is provided in the manuscript or in the Supplementary file.

Model calibration and statistical inference

From my understanding, the model appears to be calibrated to reported cases from the annual World Malaria Report. A key point here is that there can be a huge gap between what is reported, and what actually occurred – Papua New Guinea being an important example. Exact details of the statistical inference methods used for model calibration have not been provided.

Supplementary file

The Supplementary File is hard to follow. There is reference to spatially explicit models accounting for transmission between villages, but no information on how this is implemented. There is a section entitled 'Sub-patent infection and diagnostics' which describes parameters for parasite densities, but it's not clear how parasite densities are implemented in the model.

Model code

I downloaded the model code 'multispecies_model.R', but this would not run, as it needed the compiled C code 'eq0.so' which was not provided. The source code 'eq0.c' was provided which I attempted to compile myself, however this required the header 'R.h' which also wasn't provided. I found this header file online, but this file required a number of other headers. I stopped at this point.

References

1. Markell EK, Voge M: Medical Parasitology. 1965; **40** (7): 719

2. Adolphe M: Chemotherapy. *Proceedings of the 7th International Congress of Pharmacology*. 1978.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

No

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Mathematical modelling of *P. vivax* and *P. falciparum* transmission; Malaria epidemiology; Serology; Cost-effectiveness analysis; Statistics.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 21 Nov 2019

Sheetal Silal, University of Cape Town, Rondebosch, South Africa

This response has been resubmitted under the name of the lead author, as it was previously under the name of the submitting author. The response has been drafted by Dr Sheetal Silal and Professor Lisa White. Comments in italics are by the author while regular text are excerpts from the reviewer's report.

The authors appreciate the detailed comments provided by the reviewer. This review brings to light that there are different philosophies within the malaria modelling community. One philosophy favours a high level of detail and rigour for scientific extension, while the other philosophy develops models that are more concerned with supporting policy. While these philosophies are not mutually exclusive, the latter approach may require that the modeller sacrifices depth in order to provide timely support, or uses what information is available at the time to support decisions that would otherwise have been made without mathematical modelling. In general policy-makers are not at liberty to wait extended periods for models to

provide the required outputs. We feel that we share a fundamentally different philosophy from the reviewer. We respect but disagree with the reviewer's general comments, and we invite the reviewer to join us in this challenging space. There is almost always a trade-off with policy-driven research. It becomes a question of accepting it and engaging in a scientifically rigorous manner with the best available data using methods to match the time allocated, or not participating at all. We have decided to take up that challenge.

The purpose of the analysis, to project the regional path to malaria elimination, required the modelling of both Plasmodium falciparum and Plasmodium vivax malaria. Having a single species models for policy making in Asia is an incomplete and pointless activity. Programmes are focused on eliminating all malaria. While a single-species approach is relevant where Plasmodium falciparum malaria has been successfully eliminated, this is not the case for many of the Asia-Pacific settings.

We appreciate and have taken on board some of the suggestions made by the reviewer, though other comments made are factually inaccurate. It may be the case that the reviewer is willing to revise his decision in the light of our arguments, but we understand that there may a fundamental difference of opinion, and in that case we respect but do not share his opinion. We have nonetheless responded to the points that were factually incorrect for the benefit of the readers. We have ourselves pointed out the flaws in our model. All models, complex and less-so, have to make compromises, and we have done so to satisfy the purpose of the analysis in the time frame allowed.

This article attempts an extremely ambitious goal of developing and applying mathematical models of *P. falciparum* and *P. vivax* transmission (and their interactions) to 22 countries in the Asia-Pacific, and simulating the potential impact of a wide range of malaria control interventions. In casting the net so wide, I fear the authors have sacrificed depth so that it's hard to be confident in specific predictions.

As stated in the manuscript (2nd paragraph in the results section, and last paragraph in the discussion section) the authors made a conscious decision to sacrifice depth to provide timely support for decision makers. Perhaps the reviewer does not concur that this is a necessary sacrifice to be made. However, decisions will be made with or without mathematical models to support them. We argue that the utility of the approach outweighs concerns on the uncertainty around the predictions, which we have argued in the paper. The level of detail required and time taken to satisfy this reviewer's standards have not and will not be available in time for policy makers to use. The purpose of the paper, as stated in the manuscript, was not to design detailed malaria elimination strategy at a subnational level, but rather to provide broad-stroke national guidance.

I certainly see the value for making the case for malaria elimination activities in the Asia-Pacific, and the need for advocacy in this space, but great care must be taken to distinguish between which scenarios are based on the reality of up to date data and currently available interventions, and which scenarios are based on interventions that have yet to be developed (e.g. new Pf drug and new LLINs), or yet to be tested at national scale (e.g. repeated rounds of MDA).

The manuscript outlines the definition of all scenarios tested in paragraph 3 of the section “Modelling Interventions for malaria elimination” that scenarios are subdivided into four themes, stating which are extensions of current interventions, and which are hypothetical. This is again described in Figure 1: Description of scenarios modelled.

Mathematical model

The authors describe a compartmental differential equation model. Notably this does not have an individual-based structure, or incorporate age or heterogeneity in exposure to mosquito bites.

There may be a fundamental difference of opinion between the authors and the reviewer on this issue. Previous peer reviewed publications^{1, 2} have demonstrated that an IBM structure is not necessary to reproduce the qualitative predictions provided in this paper. We question whether sufficient data would ever be available to reproduce this analysis (for 22 countries) and satisfy the parameter demands of an individual-based model (IBM). This does not however negate the approach, but IBM developers should be more honest of the implied level of accuracy.

1. White LJ, Maude RJ, Pongtavornpinyo W, et al. The role of simple mathematical models in malaria elimination strategy design. *Malar J.* 2009;8:212. Published 2009 Sep 14. doi:10.1186/1475-2875-8-212
2. Brady OJ, Slater HC, Pemberton-Ross P, et al. Role of mass drug administration in elimination of *Plasmodium falciparum* malaria: a consensus modelling study. *Lancet Glob Health.* ;5(7):e680–e687. doi:10.1016/S2214-109X(17)30220-6

Transmission units

The key transmission units being modelled appear to be 22 countries in the Asia-Pacific. Within each country, transmission is enormously heterogeneous. For example, in Indonesia 141 million people live on the island of Java where there is little or no transmission, and 3.5 million live in Papua where there is intense transmission. Another key issues relates to the denominator population being modelled. For example, in China is it all 1.4 billion people, or just those who live in at risk areas? If those in at risk areas, how does this change over time?

The authors have acknowledged the heterogeneity of the Asia-Pacific and stated that they are not attempting to design sub-national strategy; hence the choice of a national spatial unit (last paragraph of the Introduction). Additionally, the denominator population being modelled is the Population at risk data sourced from the WHO World Malaria reports, as described in the Data section of the manuscript.

Parasite biology

Within the *P. vivax* research community, the evidence base for the duration of asymptomatic blood-stage infections is surprisingly weak. The authors assume a value of 130 days citing two old textbooks which I was unfortunately able to access easily^{1,2}.

In both the *P. falciparum* and *P. vivax* models, the duration of immunity in an individual without challenge is $1/\omega = 1$ year. The equations suggest this is sterile immunity, which doesn't agree with much of what is known of *Plasmodium* infection biology. This issue is likely to be particularly important for *P. vivax* when relapses are accounted for.

We have added two additional recent references from the Asia-Pacific to support the value of 130

days for asymptomatic blood stage *P. vivax* infections.

- Tripura, R., et al., *Persistent Plasmodium falciparum and Plasmodium vivax infections in a western Cambodian population: implications for prevention, treatment and elimination strategies*. *Malaria Journal*, 2016. **15**(1): p. 181.
- Nguyen, T.-N., et al., *The persistence and oscillations of submicroscopic Plasmodium falciparum and Plasmodium vivax infections over time in Vietnam: an open cohort study*. *The Lancet Infectious Diseases*, 2018. **18**(5): p. 565-572.

We do not assume sterile immunity. The equations for dR/dt and dH/dt (for *P. falciparum*) and dR/dt and dL/dt (for *P. vivax*) all have negative terms in λ , the force of infection.

Additionally the model diagrams for both species show arrows leaving R, H and L and entering the infectious compartments.

Time scale

The time scales for simulation seem a little out of date. The model is calibrated to data from 2010 – 2015, with simulations provided from 2015 – 2030, and changes in interventions occurring in 2017. It's now midway through 2019. The 2018 World Malaria Report was published in November 2018, containing data up as far as 2017.

The purpose of the study was to develop a model whose results would inform an investment case³. The timeframe of the analysis was chosen to correlate directly with the investment case. We have added a sentence in the manuscript to reflect this.

1. Shretta R, Silal SP, Celhay OJ et al. *Malaria elimination transmission and costing in the Asia-Pacific: Developing an investment case [version 1; peer review: awaiting peer review]*. *Wellcome Open Res* 2019, 4:60

Drug treatment

The drug combinations used for MDA are not specified. Many countries in the Asia-Pacific have *P. vivax* radical cure with primaquine in their national treatment guidelines, but few routinely administer it due to the absence of easily available testing for G6PD deficiency.

*This point is already made in the Discussion section of the manuscript as 'Radical cure is incorporated into the mathematical model through the adoption of a 14-day regimen of primaquine for all countries from the year of adoption specified in the World Malaria Reports. Though primaquine was adopted as policy in all countries, full-scale implementation is hampered by poor patient compliance with its 14-day treatment as well as the risk of severe haemolysis in individuals with deficiency of the enzyme glucose-6-phosphate dehydrogenase and the associated logistical and administrative burden of testing^{53,55}. Although all 22 countries have adopted primaquine to treat *P. vivax* in policy, it was not known which countries were successfully implementing the treatment. The model assumes that primaquine was used to treat *P. vivax* infections (with testing for G6PDd) from the year of adoption stated in the World Malaria Reports.' With respect to drug combinations, while we acknowledge that candidate drugs for MDA may differ between countries, the intervention was modelled using the characteristics of DHA-Piperaquine. This detail has been added to section describing MDA in the paper.*

The incorporation of G6PD deficiency in the *P. vivax* transmission model is unclear: it appears to only be accounted for after treatment is administered.

The 'Plasmodium Vivax sub-model' section of the Supplementary file states 'The G6PDd proportion

of the population has a reduced probability of clinical infection compared to the non-G6PDd proportion of the population. When primaquine treatment is introduced, those diagnosed with P. vivax can receive a test for G6PDd and are given Primaquine depending on the test outcome subject to test sensitivity' showing that G6PD deficiency is captured before infection and determines the treatment path subject to test sensitivity.

The 'Single Dose New Pv Treatment' that is referenced is presumably tafenoquine which was licensed by the US FDA in July 2018.

This licensing occurred after the period of analysis for the manuscript. We have added a line in the paper to note it.

Intervention models

No details of how intervention models were implemented is provided in the manuscript or in the Supplementary file.

Thank you for this comment. We have added detail on the modelling of interventions in the supplementary file.

Model calibration and statistical inference

From my understanding, the model appears to be calibrated to reported cases from the annual World Malaria Report. A key point here is that there can be a huge gap between what is reported, and what actually occurred – Papua New Guinea being an important an example. Exact details of the statistical inference methods used for model calibration have not been provided.

The manuscript states that the model is calibrated to disease burden estimates (line 1 of the Model Calibration section) and not reported incidence for precisely this reason. The authors also describe the computation of the burden estimates, based on incidence and estimates of reporting and refer to a partner manuscript in this collection where this is presented in detail (4). Additionally, the World Malaria Report is the gold standard source of data for international policy making. The authors are curious to know what dataset the reviewer proposes we use for 22 countries in Asia-Pacific.

1. Maude RJ, Mercado CEG, Rowley J et al. Estimating malaria disease burden in the Asia-Pacific [version 1; peer review: 1 approved with reservations]. Wellcome Open Res 2019, 4:59

Supplementary file

The Supplementary File is hard to follow. There is reference to spatially explicit models accounting for transmission between villages, but no information on how this is implemented. There is a section entitled 'Sub-patent infection and diagnostics' which describes parameters for parasite densities, but it's not clear how parasite densities are implemented in the model.

The Supplementary file has a section entitled 'Spatial Heterogeneity' that describes how distance between patches/countries is incorporated in the force of infection. The formula for the resultant force of infection is also given. As described in the section 'Sub-patents and diagnostics', the parasite densities are used to compute test sensitivities and the duration of sub-patent infections.

These estimates are incorporated in the model as estimates of sensitivity for diagnostics used by countries.

Model code

I downloaded the model code 'multispecies_model.R', but this would not run, as it needed the compiled C code 'eq0.so' which was not provided. The source code 'eq0.c' was provided which I attempted to compile myself, however this required the header 'R.h' which also wasn't provided. I found this header file online, but this file required a number of other headers. I stopped at this point.

This has not been a problem on previous trials of downloading code from the repository. We have uploaded eq0.dll and eq0.so along with eq0.c to mitigate this issue.

Competing Interests: none
