RESEARCH ARTICLE

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

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Abstract

Background: The Asia-Pacific region has made significant progress in combating 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 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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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 elimination3,4.

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 unchanged6. 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 them3.

In the past, economic evaluations and costing of interventions against disease have commonly been conducted using decision trees or Markov models1. 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 setting9,10 and since 2010, a number of dynamic models of Plasmodium vivax malaria transmission have been published11–19. Recently published models of both P. falciparum and P. vivax malaria have employed dynamic mathematical methods10,20 and statistical techniques11–21. 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.22 and the computer application developed to showcase the project results, the METCAP application is presented in Celhay et al.23.

Methods

Model generation
A dynamic compartmental model for P. falciparum malaria transmission was developed based on previously published models11–13,18–20. 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 Data

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 parasitemia 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.

2. **Triggering**
   It has been observed in many studies that clinical *P. falciparum* infections are often followed by *P. vivax* infection. It has been hypothesized that the subsequent appearance of *P. vivax* implies that a *P. falciparum* episode reactivates *P. vivax* hypnozoites. 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* malaria. 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* cases. 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 R 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.

**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. 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)

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 2015. This was used by Maude et al. to derive estimates and ranges of the clinical burden of disease for both *P. falciparum* and *P. vivax* malaria from 2000 to 2015.
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 data.

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. 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.

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

![Figure 1. Description of scenarios modelled to assess if elimination could be achieved by 2030.](image)

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.
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. 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 2012, 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 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, 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.

**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 2030\(^1\). 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 years\(^1\). 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 drugs\(^1\). The region is dominated by *P. vivax* malaria, accounting for more than 75% of the global burden\(^1\). The misconception of *P. vivax* malaria as benign has also contributed to it being neglected as a scientific, clinical, and public health issue\(^1\). The variation in malaria burden with
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 PfDrug. All scenarios are considered ‘less effort’ without the addition of Mass Drug Administration.
<table>
<thead>
<tr>
<th>Country</th>
<th>Minimal scenario for elimination</th>
<th>Range</th>
<th>National Goal</th>
<th>Regional Goal</th>
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</thead>
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<tr>
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<td>2030</td>
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<tr>
<td>Bangladesh</td>
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<td>2025 (2024,2029)</td>
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<td></td>
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<tr>
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<td>New LLINs with MDA</td>
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</tr>
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<td>Single dose new Pv treatment with ITN scale-up</td>
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<td>2025</td>
</tr>
<tr>
<td>India</td>
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<td>2030</td>
<td></td>
</tr>
<tr>
<td>Indonesia</td>
<td>Effective Usage with MDA</td>
<td>2025 (2022,2028)</td>
<td>2030</td>
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<td>Lao PDR</td>
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<td>2023 (2019,2029)</td>
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<tr>
<td>Myanmar</td>
<td>New Pf drug with ITN scale-up and MDA</td>
<td>2025 (2024,&gt;2030)</td>
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<tr>
<td>Nepal</td>
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<td>Pakistan</td>
<td>Effective Usage with ITN scale-up and MDA</td>
<td>2022 (2021,2030)</td>
<td>2030</td>
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<td>Papua New Guinea</td>
<td>Effective Usage with MDA</td>
<td>2025 (2025,2028)</td>
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<td>Thailand</td>
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<td>2025</td>
<td>2030</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>Effective Usage</td>
<td>2024 (2022, 2027)</td>
<td>2030</td>
<td>2030</td>
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Table 1. Minimum elimination package per country with national and regional goals for year of elimination.

*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 system. 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.

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 sustained. 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. Although all 22 countries have adopted primaquine to treat Plasmodium 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 G6PD deficiency) 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. 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 response. 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.

**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 strategies. 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 Plasmodium 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. The set of annual reports from 2008 onwards can be accessed at [http://www.who.int/malaria/publications/world_malaria_report/en/](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.2575474](https://doi.org/10.5281/zenodo.2575474).

Data are available under a [CC0 1.0 Universal license](https://creativecommons.org/publicdomain/zero/1.0/).

**Software availability**

Model source code available from: [https://github.com/sheetalsilal/METCAP](https://github.com/sheetalsilal/METCAP)

Archived source code at time of publication: [https://doi.org/10.5281/zenodo.2575474](https://doi.org/10.5281/zenodo.2575474).
Asia (106698/Z/14/Z). The authors were not paid to write this manuscript.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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References

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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.

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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 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?

**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 an 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**
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.