Malaria in the Asia-Pacific: Modelling the current and potential impact of artemisinin resistance and its containment
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The Australian Government is hosting the Malaria 2012: Saving Lives in the Asia-Pacific conference in Sydney, Australia from 31 October to 2 November 2012. The conference aims to reinvigorate progress in malaria control and elimination in the Asia-Pacific region and to agree actions to urgently tackle resistance to artemisinin. The Australian Agency for International Development (AusAID) has commissioned five thematic papers to inform presentations and discussions during the conference.

The analysis in these papers examines progress to, and efforts needed to achieve the goals set by the global malaria community including the long term aim of malaria elimination. The papers look at how and what is needed to accelerate progress to achieve a 75 per cent reduction in malaria deaths and cases by 2015 over a 2000 baseline, agreed by the World Health Assembly in 2005 and re-confirmed in 2007.

The five papers in the series are:

1. **Malaria in the Asia-Pacific: burden, success and challenges** which summarises the current burden, successes and challenges in malaria control and elimination in the Asia-Pacific region and discusses the major policy implications for countries and regional development partners.

2. **Malaria in the Asia-Pacific: Challenges and opportunities for sustainable financing** describes some of the challenges facing the region as it moves towards greater regional self-sufficiency in financing malaria control and elimination.

3. **Malaria in the Asia-Pacific: Challenges and opportunities for access to quality malaria medicines and other technologies** summarises the key issues and challenges to improving quality and access to malaria medicines and commodities in the Asia-Pacific region, and highlights reducing the risk of artemisinin resistance.

4. **Malaria in the Asia-Pacific: Modelling the current and potential impact of artemisinin resistance and its containment** describes the global impact of artemisinin resistance should artemisinin combination therapies and artemisinin monotherapies lose their effectiveness. The paper also focuses on the health, economic and development impact of increased levels of artemisinin resistance in the Asia-Pacific region.

5. **Malaria in the Asia-Pacific: The role of the private sector in ensuring equity and access to services** provides an overview of the private sector operating in malaria in the Asia-Pacific region and describes key challenges and opportunities for engaging the private sector, including best practice from the region and elsewhere.

This paper has been produced as a background paper for the Malaria 2012: Saving Lives in the Asia-Pacific Conference by the AusAID Health Resource Facility (HRF) managed by Mott MacDonald Australia Limited. The content does not necessarily reflect Australian Government policy.

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### Acronyms

<table>
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<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>ACT</td>
<td>Artemisinin-based combination therapy</td>
</tr>
<tr>
<td>AP</td>
<td>Asia-Pacific</td>
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<tr>
<td>DALY</td>
<td>Disability adjusted life year</td>
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<tr>
<td>GDP</td>
<td>Gross domestic product</td>
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<tr>
<td>HC</td>
<td>Health centre</td>
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<tr>
<td>HTI</td>
<td>High Transmission Intensity</td>
</tr>
<tr>
<td>ITN</td>
<td>Insecticide treated nets</td>
</tr>
<tr>
<td>LLIN</td>
<td>Long lasting insecticide treated nets</td>
</tr>
<tr>
<td>LLIHN</td>
<td>Long lasting insecticide treated hammock nets</td>
</tr>
<tr>
<td>LTI</td>
<td>Low Transmission Intensity</td>
</tr>
<tr>
<td>MDA</td>
<td>Mass drug administration</td>
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<tr>
<td>MFT</td>
<td>Multiple first line therapy</td>
</tr>
<tr>
<td>MMW</td>
<td>Mobile Malaria Worker</td>
</tr>
<tr>
<td>MSAT</td>
<td>Mass screening and treatment</td>
</tr>
<tr>
<td>PIPR</td>
<td>Plasmodium falciparum parasite rate</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
</tr>
<tr>
<td>PQ</td>
<td>Pre-qualified/pre-qualification</td>
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<tr>
<td>RDT</td>
<td>Rapid diagnostic test</td>
</tr>
<tr>
<td>SSA</td>
<td>Sub-Saharan Africa</td>
</tr>
<tr>
<td>US$</td>
<td>United States dollars</td>
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<tr>
<td>VMW</td>
<td>Village Malaria Worker</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WWARN</td>
<td>World-wide antimalarial resistance network</td>
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<td>$</td>
<td>Unless stated otherwise, all figures are in 2012 US dollars (USD).</td>
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Executive Summary

Key messages

1. The expanded use of artemisinin-based combination therapies (ACTs) has played a major role in reducing malaria illness and deaths worldwide. The continued efficacy of ACTs is critical for ensuring that gains made are not reversed and for the eventual elimination of malaria. Future progress in malaria control is thus jeopardised by the emergence of resistance to artemisinin and ACTs.

2. The health and economic impacts of widespread artemisinin and ACT resistance are likely to be substantial. Global malaria mortality could increase by 25 per cent; productivity losses during illness and following death may exceed US$4 billion annually; and the direct medical costs associated with re-treatment and a rising number of cases of severe malaria (due to the spread of resistance) is likely to be over US$30 million annually. Costs of the introduction of an alternative treatment could exceed US$120 million for the policy change alone, while alternative therapies, once available, will likely cost in excess of US$100 million annually for each $ increase in unit cost over current ACT prices.

3. Findings from modelling the spread and containment of ACT and artemisinin resistance in the Asia-Pacific region suggest that the only strategy likely to contain resistance is the elimination of *falciparum* malaria (one of the two most prevalent species of malaria in the region infecting humans).

4. Modelling different combinations of interventions in different transmission settings demonstrates the feasibility of, and time required to reach elimination. Switching between alternative ACTs is a prerequisite for elimination irrespective of transmission setting.

5. Elimination in low and high transmission settings is feasible using a range of strategies including increasing coverage of insecticide treated bednets (ITN), mass drug administration (MDA); mass screening and treatment (MSAT); and adding a single dose of the drug primaquine to routine treatment.

6. Cost effectiveness modelling suggests that in higher transmission settings even the most costly combination of interventions is justifiable, as the local health gains achieved alone justify the higher expenditure. In low transmission settings the health gains for the local population will be lower, however the potential impact of spreading resistance globally would strongly support a committed investment in costly containment measures.

Overview

This paper describes the global impact of artemisinin resistance should ACT and artemisinin monotherapies lose their effectiveness. The paper also focuses on the emergence of artemisinin resistance in the Asia-Pacific region and considers the combination of interventions, costs, and effectiveness of measures needed to contain resistance in different transmission contexts.
Background
In the last decade, very significant progress has been made in tackling malaria. The expanded use of ACTs forms the cornerstone of global malaria control and elimination efforts, playing a major role in reducing malaria illness and deaths worldwide. ACTs are the recommended first line treatment for uncomplicated malaria and their continued efficacy is critical for the future success of malaria control and for protecting the lives of millions of vulnerable people across the world.

Drug resistance
Many antimalarial medicines have lost their efficacy due to drug resistance. Artemisinin resistance has also been detected, initially in Cambodia in 2007 and then more recently confirmed on the Thai-Myanmar border. So far, resistance has manifested as a delay in time taken to fully clear infected parasites from the body, with minimal treatment failure. However, without further action, it is entirely possible that resistance to both artemisinin and the partner drugs which comprise widely-used ACTs will follow shortly. If ACT resistant malaria parasites do emerge and spread, there will be severe global public health and economic consequences.

The prospects of growing ACT resistance have captured the attention of policy makers, implementers and researchers, and efforts to contain the spread of resistance are already in place in Cambodia and Thailand. But the effort is insufficient so far and, more importantly, does not include all countries where resistance has been identified. In Myanmar, with the largest malaria burden in the region, artemisinin resistance has also been identified. But Myanmar has received very little support to contain the spread of resistance and is potentially a route for resistant parasites to spread to other regions. Resistance can only be controlled when measures are taken in the entire region where it is present.

Multi-site clinical studies are also underway to identify artemisinin resistance elsewhere, but these may not provide data in sufficient time for a well-prepared and adequate response.

Mathematical modelling
Until more robust evidence becomes available, mathematical modelling has a critical role to play in helping policy makers to develop an appropriate and timely response to the threat of emerging artemisinin resistance. This paper presents two models:

- Model 1: describes the global impact of artemisinin resistance should ACTs and artemisinin monotherapies lose their effectiveness. It is not certain that artemisinin resistance will evolve in the way presented, although such a scenario is more likely if stronger containment measures are not implemented.

- Model 2: focuses specifically on areas where artemisinin resistance has emerged and considers its development and the cost and effectiveness of containment measures.

It is important to emphasise that the uncertainties in this analysis are great and the findings speculative.

Analysis
Findings from the first model indicate the possible global health and economic impacts resulting from substantial ACT resistance will be great: an estimated 150,000 additional deaths annually, direct medical costs of more than US$30 million, and productivity losses of approximately US$4 billion per annum. The total funding requirement for a global switch to a new antimalarial medicine is expected to be in the range of US$120 million for the policy change alone. Alternative therapies, once available, are likely to cost more than the current ones. Each US$1 increase in unit cost will likely lead to more than US$100 million in medicine costs annually. The largest share of these costs will
likely be incurred in the Asia-Pacific region due to its large population.

Greater regional and international cooperation will be required to minimise the chances of resistance spreading from the Asia-Pacific region to Africa where the impact of resistance is likely to be much greater.

Findings from the second model have been used to identify the critical determinants of the spread of artemisinin resistance. Population movement was found to be an important factor in contributing to resistance, indicating that programs focusing on migrant and hard to reach groups could be beneficial in slowing the spread of resistance to artemisinin. While switching between ACTs with different partner medicines could also delay the onset of resistance to ACTs.

Elimination of Plasmodium falciparum malaria in areas where artemisinin resistance is present is the only strategy that is predicted to contain it.

Through using a combination of interventions, local elimination of malaria in low transmission settings is feasible. Elimination in higher transmission settings is also achievable through MSAT, MDA and a malaria vaccine, once available.

Conclusion

This analysis confirms that we must take action. The potential costs and mortality associated with artemisinin resistance shown here are conservative estimates; if artemisinin resistance spreads the actual impact is likely to be much greater. The models suggest that affordable measures taken early should be effective in decreasing the probability of such a scenario unfolding.
Artemisinin derivatives are central to the management of malaria. Artemisinin-based combination therapies (ACTs) are recommended for first line treatment of uncomplicated malaria across the malaria endemic world. With The Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) funding and other external support, many countries in sub-Saharan Africa (SSA) and the Asia-Pacific region have had considerable success in deploying ACTs in public health facilities. For severe malaria, the World Health Organization (WHO) now recommends artesunate which has been shown to offer significant survival advantage over quinine.

The emergence of artemisinin resistance therefore threatens to undo much of the progress made in malaria control and elimination over the last decade. The magnitude of this threat is not well defined and the evidence to guide policy on the measures required to contain it is scarce. The aims of this paper are to describe the potential health and economic impact of missing the opportunity to contain artemisinin resistance during these early days of emergence and to assess the relative cost-effectiveness of containment strategies. If containment is successful, a substantive reduction in malaria mortality will follow, extending the reach of ACTs for the treatment of clinical malaria and use of artesunate for severe malaria. If containment efforts fail, the real gains of the last decade as well as future potential gains could be lost.

Mathematical modelling is used to achieve the aims of this paper. A mathematical model is a simplified description (in mathematical language) of a system. Models can combine knowledge on multiple interacting mechanisms of the system and available data in a logical framework. Mathematical models are used to aid understanding of the systems in question and to make predictions on the future behaviour of these systems.

Section 2 describes the current and predicted future forms of artemisinin resistance. Section 3 describes a model-based assessment of the public health and economic impact of artemisinin resistance. This provides a description of the global impact of artemisinin resistance, should ACTs and artemisinin monotherapies lose their effectiveness. The paper then moves on in Section 4 to focus specifically on areas where artemisinin resistance has emerged, to consider how it is likely to develop. Mathematical models are used to explore the potential future increases in malaria incidence if no action is taken using the locations on the Thai-Cambodian border and the Thai-Myanmar border where artemisinin resistance has been confirmed. The models also demonstrate the potential effects of migration of individuals infected with artemisinin resistant malaria into susceptible areas and the possible increases in the incidence of malaria that would follow.

The same models are then used in Section 5 to perform a cost-effectiveness analysis of an example set of containment strategies. In this way the model is used to assess the effectiveness and costs of different containment strategies that are currently being considered. Reassuringly the predictions suggest that local elimination of
malaria in areas of low transmission, such as those where resistance has so far been documented, could be feasible with a range of possible interventions. Finally Section 6 summarises the future research goals for the modelling of the impact and containment of artemisinin resistance. Annex 1 provides further information on the characterisation and measurement of artemisinin resistance. Annexes 2 and 3 provide information on the values and methodology deployed for the models in Section 2. The details of the model used in Sections 4 and 5 can be found in Annex 4.
2. Artemisinin resistance versus ACT resistance

To predict the spread and containment of artemisinin resistance, a number of competing issues and effects must be considered. Firstly, interventions that are executed as early in a disease outbreak as possible are more likely to be effective and models developed for aiding the design of such strategies should be evidence-based. In the case of emerging artemisinin resistance, the amount of evidence available will increase with time, but the likelihood of success of containment strategies will decrease with time and so there is a trade-off in the level of evidence on which to base models and the window of opportunity for intervening successfully. Secondly, the lower the transmission rate, the faster resistance spreads, due to low immunity levels leading to increased treatment seeking and higher selective pressure, so there is a trade-off between reducing transmission and delaying spread of resistance. Thirdly, using artemisinin-based combination therapy at high coverage either as routine treatment or in mass-interventions can result in a reduction in the numbers of artemisinin resistant malaria cases but this will be accompanied by an increase in the proportion of infections that are resistant. Since there are no known interventions that will reduce the proportion of resistant infections in a given population, the only option is to reduce the numbers of resistant infections to zero. This means local elimination of all Plasmodium falciparum (P. falciparum) malaria, as a containment strategy.

When the term “artemisinin resistance” is used, it is important to distinguish this from “ACT resistance.” The current definition of “artemisinin resistance” is based on a reduction in the clearance rate of asexual parasites from the blood during treatment with artemisinin monotherapy or an ACT. Preliminary results on characterising and measuring artemisinin resistance can be found in Annex 1.

Artemisinin resistance is associated with elevated treatment failure rates under monotherapy, but not necessarily under ACT since the partner medicine would still be effective against such infections. The novel emergence of this resistance is assumed to be rare. “ACT resistance”, on the other hand, would be infections that have simultaneous resistance to both artemisinin and the ACT partner medicine. There are as many potential types of ACT

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4 Unless there is a fitness cost of resistance (currently unknown).
5 Maude, R. J., et al., ‘The last man standing is the most resistant: eliminating artemisinin-resistant malaria in Cambodia’, Malaria Journal 8 (2009), 31.
resistance as there are partner medicines and the novel simultaneous emergence of this resistance would be many orders of magnitude less likely than for artemisinin resistance alone. This type of resistance would be associated with much higher failure rates since both components of the ACT would not be functioning. This type of resistance has been modelled before to demonstrate the potential of multiple first line therapies (MFT) in delaying the spread of resistance.\textsuperscript{7} What is explored in this paper is the risk that parasites that are already “artemisinin resistant” evolve partner drug resistance and therefore become “ACT resistant”. This event can be relatively frequent depending on the partner medicines and the pre-existence of artemisinin resistance and this transition is the main public health and economic risk.

Resistance to previous antimalarial treatments is believed to have resulted in considerable excess mortality. In this section we describe the potential health and economic losses that could be associated with ACTs succumbing to a similar fate to their predecessors. There are currently few indications of clinical failures in ACT treatment, and there is considerable benefit in combination therapies in terms of reduced risk of emergence and spread of resistance, however the possibility of this occurring with ACTs cannot be dismissed.

The following analysis provides a snapshot of the consequences of ACT resistance should this occur, starting from a point where a proportion of patients fail their ACT treatment. Most patients who fail their treatment recover spontaneously or access second line treatment, although a small proportion will develop severe malaria. In the absence of effective treatment, the mortality rate for severe malaria is high and the majority of malaria deaths are believed to occur outside of health facilities, often unrecorded. For patients with access to in-patient care, the WHO and the majority of endemic countries recommend the use of artesunate, after a consistent survival advantage over quinine was documented in the two largest clinical studies of in-patient treatment for severe malaria. This advantage is ascribed to the artemisinins’ unique ability to rapidly clear the parasite biomass. The 2010 WHO report on antimalarial resistance, however, states that “In areas where artemisinin resistance is confirmed…administration of parenteral artemisinin-based monotherapy may no longer be appropriate” signalling a return to quinine, the only other currently available therapy for severe malaria.

These possible consequences for artemisinin resistance – a higher failure rate in ACTs and the loss of the advantage of artesunate for severe malaria, can have wide reaching health and economic implications, including:

1. A higher number of clinical cases due to increased transmission
2. An increased incidence of severe cases following higher treatment failure rates in uncomplicated malaria
3. A higher mortality rate for severe malaria as artesunate loses its efficacy, or equally as clinicians revert to the use of quinine

Reference:
4. Cost of diagnosis and treatment of primary infections increasing with higher incidence
5. Cost of repeat diagnosis and second line therapy in treatment failures
6. Hospitalisation costs for increased incidence of severe malaria
7. Cost of switching to alternative first line treatments as these become available, including
   › the incremental cost of the new medicines
   › cost of policy change
8. Productivity losses imposed by higher morbidity and mortality
9. The impact of continued transmission and extended time to elimination on gross domestic product (GDP) growth
10. The added costs of maintaining malaria prevention where elimination is postponed.

The analysis in this section compares the health and economic outcomes that could occur over a five-year period, which is an estimate of the minimum duration from when ACT resistance becomes widespread until replacement treatments are developed and deployed, in the following scenarios with effective artemisinin based treatments and in the presence of widespread ACT resistance.

This comparison allows for the assessment of the impact of ACT resistance if containment of artemisinin resistance fails. Details on the methodology can be found in Annex 2 and summarised in Section 3.1.

### 3.1 Model predictions

#### Excess clinical and severe malaria cases

The number of excess clinical cases due to ACT resistance was estimated at 9.6 million clinical cases per annum globally, or 47 million over the five-year period (interquartile range is 29 to 58 million cases). This accounts only for patients who fail their first treatment, and not for any increases in transmission. Almost 85 per cent of these cases are expected to occur in SSA, 13.5 per cent in the Asia-Pacific region and the remainder in the Americas. The excess number of severe cases was approximately 3.5 million (interquartile range is 3.1 to 3.9 million cases), with 89 per cent occurring in SSA. The higher proportion of severe cases in SSA as compared with uncomplicated cases is due to the higher prevalence of *P. falciparum*.

#### Excess mortality due to ACT resistance

Figure 1 overleaf shows the estimated annual mortality in a scenario where ACTs and artesunate are effective (green bars), as compared with one where these advantages are lost (red bars). On the right hand side Figure 1 also shows the excess annual mortality due to ACT resistance over a five-year period until an alternative treatment is in place. These estimates will vary linearly with the number of years until an alternative treatment is developed and deployed. It is also likely that alternative ACTs would be rolled out in the interim where existing ones are failing which could provide at least temporary gains. This will incur the costs of policy change (described below) and could also require considerable time to implement.
Figure 1: In the graph on the left are annual mortality estimates in the two modelled scenarios, where ACTs are effective (in green) and in the presence of ACT resistance (in red). In the graph on the right is the excess mortality due to ACT resistance over five years.

Figure 2 shows the geographical spread of these excess deaths in absolute numbers. These data are described in detail in Annex 3.

**Figure 2: Annual excess mortality due to ACT resistance compared with a scenario of effective artemisinin therapies, in absolute numbers**

One of the critical parameters for which data are scarce is the probability of patients with treatment failure becoming severely ill, initially estimated to be 4 per cent for low transmission settings and 3 per cent for high transmission ones. The baseline values used were at the lower end of expert opinion and were therefore varied by decreasing and increasing them by 50 per cent, with the consequences shown in Figure 3. \(^{15,16}\) Results so far are also conservative in that they have not accounted for one of the main anticipated consequences associated with the


spread of resistance – the increase in incidence due to extended infections and the failure of artemisinin treatment to control the infectiousness of individuals infected with resistant parasites. The graph below shows the anticipated excess mortality with respect to changes in the incidence of malaria. The excess mortality associated with ACT resistance per year across this range of parameters was 0.2 to 1.6 million cases over five years.

Figure 3: Excess mortality due to ACT resistance with variable incidence of malaria and probability of treatment failures becoming severely ill. In black are the series using the baseline estimates.

Economic impact of ACT resistance
The direct medical costs associated with the re-treatment of patients who fail their ACT include those for a diagnostic test to confirm failed treatment due to the regrowth of parasites in the infected individual using a malaria rapid diagnostic test (RDT) or microscopy, and a secondary treatment. The global costs for these are projected to exceed US$100 million over the five years until an alternative treatment is available. For patients who deteriorate to severe illness there are substantial costs incurred by hospital admissions, totalling almost US$60 million. The regional assessments and interquartile range are shown in Figure 4.

Figure 4: The direct medical costs associated with ACT resistance and the cost of policy change to alternative treatment once these become available
The introduction of a new first line therapy, once available, will require a change in national policies for the management of malaria with support and training programs to facilitate its deployment. Mulligan et al. conducted the only detailed estimate for the costs of a national revision of antimalarial treatment guidelines, in this case for Tanzania in 2002.\textsuperscript{17} Here, these findings are taken and, after inflationary adjustments and classification as either fixed costs or variable ones (assumed to be correlated with population size), applied to malaria endemic countries. The total funding requirement for a global switch to a new antimalarial is expected to be in the range of US$120 million. The largest share of this would be incurred in the Asia-Pacific region due to the larger population size.

Historical trends would suggest that new antimalarial medicines, as with most treatments, are costlier than the failing medicines they replace. Even modest incremental costs will result in considerable excess expenditure, dependent also on the achieved coverage, as show in Figure 5.

Figure 5: Annual incremental cost of treatment with a new first line antimalarial by unit cost and coverage for sub-Saharan Africa

The direct expenditures shown so far are dwarfed by the productivity losses due to excess morbidity and mortality over the five-year period. Globally, these could exceed US$15 billion. Productivity losses due to mortality are almost 90 per cent of the total, and the remainder attributed to morbidity during episodes of uncomplicated and severe malaria. The regional breakdown and interquartile range are shown in Figure 6.

3.2 Discussion

This analysis does not project how artemisinin resistance is likely to spread or portray the most probable scenario that is likely to unfold. Rather, this is an assessment of the impact of artemisinin-based therapies facing similar failure rates as all previous first line antimalarial medicines. Many of the key parameters here are pervaded by uncertainty, leading to wide error bars on most findings, although the methods and point estimates chosen were conservative.

The lower estimates for mortality associated with artemisinin and ACT resistance are approximately 150,000 deaths annually globally and almost US$160 million for the direct medical costs alone. The longer term productivity losses are two to three orders of magnitudes higher. The costs of replacing the artemisinins will also be considerable, most likely exceeding US$120 million for the policy change, and an undetermined although likely much higher figure for the medicines themselves. Direct household costs have not been included although have been shown to be substantial.\textsuperscript{18} The spread of artemisinin and ACT resistance will also increase transmission and threaten elimination strategies allowing malaria to continue its demonstrated drain on macroeconomic growth.\textsuperscript{19,20} Delays in achieving elimination are also important, not just because of the additional costs incurred to prolong malaria control activities, but also because other current malaria control tools, such as pyrethroid insecticides for nets are likely to need replacement in a few years.

There are extensive limitations to this analysis relating to both the model structure and parameter uncertainty, therefore wherever possible conservative estimates were used.

The main limitation is the model’s static structure, which compares two distinct scenarios (ACTs being effective in one and a homogenous 30 per cent failure rate in the other) but does not simulate the transmissions between them nor intermediate phases. A global malaria transmission model that would be required for this has not yet been successfully created, to our knowledge, and it was not feasible to attempt this here. The model therefore assumes critically that the incidence of malaria in the scenario where resistance has spread will resemble its current levels and will remain fixed over the five-year period for which the mortality and costs are assessed. In addition to the extensive uncertainty surrounding incidence for previous years, projections of future trends are challenging, with transmission being influenced by the availability of ACTs and other interventions, as well as a range of factors including economic, environmental and demographic changes. The spread of artemisinin and ACT resistance will itself most likely be a product as well as a cause of changes in transmission.

For the annual incidence of uncomplicated malaria, the WHO data for probable and confirmed malaria cases in 2010 are used. They are the lower end of current estimates and may grossly underestimate the actual incidence.\(^{21}\) The mortality figures on which the probability of treatment failures progressing to severe malaria and death were based also at the lower end of current estimates. Using higher incidence and mortality rates would result in much higher projections of excess mortality due to ACT resistance.

The analysis assumes a period of five years for the time from the point where artemisinin-based treatments are failing to the deployment of a new class of effective treatments. This is considerably less than historical precedents would suggest.\(^{22}\) This figure will ultimately be determined by the interactions between routine diagnostic and treatment practices for malaria, the presence and effectiveness of resistance-containment strategies and the pipeline for the development of new treatments. It is also probable that alternative ACTs would be introduced if existing ones are failing, mitigating some of the potential impact.

Coverage of ACT is assumed to be at 40 per cent. The potential benefits of effective artemisinin treatments could therefore be much higher, as would the loss of these due to resistance. It could be argued that the cost of artemisinin resistance should indeed reflect the loss of the full potential benefits of artemisinin that are forgone, and not only those that are materialised under partial coverage. The approach taken therefore is also conservative.

The productivity losses were based on GDP per capita while in reality malaria is known to be correlated with poverty. Using minimum wages instead of GDP per capita could have resulted in estimates of approximately one third of those presented here, which are still in the range of US$5-8 billion over the five-year time horizon.\(^{23}\)

This analysis has assumed a homogenous loss of artemisinin efficacy across the endemic world. In reality the spread and impact of artemisinin resistance followed by ACT resistance, should it occur, will be extremely variable and dependent on transmission intensity, partner medicine, health system preparedness and many other variables. As in the case of the artemisinins, resistance to most previous antimalarial medicines were first documented in Southeast Asia. Stable high transmission and relatively low use of artemisinin monotherapy might lead to slower spread within SSA. For countries in closer proximity to the known epicentre of artemisinin resistance such as Myanmar, Bangladesh and India, with large


\(^{23}\) Saget, C., *Fixing Minimum Wage Levels in Developing Countries*, (Jakarta, ILO, 2006).
populations at risk of *P. falciparum* and areas of unstable transmission, artemisinin resistance could pose a particularly high threat. Malaria related incidence and mortality in India was recently estimated in one study to be of an order of magnitude higher than previously estimated. Whilst there is controversy on the estimation methods used, the higher estimate would mean that the impact of resistance could be similarly higher than estimated here, implying that much of the total burden would shift to the Asia-Pacific region.

This analysis, albeit highly speculative, provides a set of ballpark figures for the excess mortality and economic losses that could follow widespread resistance to artemisinin-based therapies. These figures in themselves cannot be used to identify the optimal levels of investment that could be justified to contain artemisinin resistance, as this would require further estimates for the probability that a scenario such as this is likely to unfold. The magnitude of the threat posed by the spread of artemisinin resistance followed by ACT resistance does, however, suggest that even if this is a remote possibility, considerably higher attention and investment in delaying or eliminating its possible emergence than are currently being provided are justified. In the following sections the focus is on key determinants of the likelihood of artemisinin resistance developing further into ACT resistance, and the most cost-effective measures to contain this.

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A standard prediction from all mathematical models that the authors are aware of is that resistance will spread more slowly if the first line therapy is an ACT treatment rather than artemisinin monotherapy. This is because the partner medicine reduces the probability of artemisinin resistant infections transmitting. There are a number of ACT partner medicines and, for simplicity, they have been split into four types relevant to resistance risk (see Table 1).

### Table 1: Classification of partner medicine types. PK= pharmacokinetic

<table>
<thead>
<tr>
<th>type</th>
<th>per parasite mutation rate</th>
<th>PK - elimination rate</th>
<th>medicines of this category</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>High (around 1 in $10^9$)</td>
<td>Fast (after about 3 weeks)</td>
<td>atovaquone-proguanil (Malarone™)</td>
</tr>
<tr>
<td>2</td>
<td>High (around 1 in $10^8$)</td>
<td>Slow (after about 6 weeks)</td>
<td>mefloquine</td>
</tr>
<tr>
<td>3</td>
<td>Low (around 1 in $10^{13}$)</td>
<td>Fast (after about 3 weeks)</td>
<td>lumefantrine, amodiaquine,</td>
</tr>
<tr>
<td>4</td>
<td>Low (around 1 in $10^{13}$)</td>
<td>Slow (after about 6 weeks)</td>
<td>piperazine, pyronaridine</td>
</tr>
</tbody>
</table>

This effect can be illustrated with a model simulation of the treatment and containment changes in Pailin, Western Cambodia. For details of the model used, see Annex 4.

---

First line treatment predominantly (90 per cent) with artemisinin monotherapy is assumed until the year 2000 when most (75 per cent) treatments were ACT. In 2004, the predicted percentage of treated cases increased due to containment measures, this combined with the distribution of insecticide treated nets (ITN) is predicted to result in a decrease in the incidence of clinical *P. falciparum* malaria. For the ACT, each of the types 1 to 4 were simulated and the model predicts a faster spread of resistance if ACTs with fast mutation rate partner medicines (types 1 and 2) are used (Figure 7, top graph).

In the next simulation to replicate the observed dynamics in Mae Sot, Western Thailand, a constant influx of artemisinin resistant infections between 1970 and 2025 was assumed (this could be considered as importation of cases due to population movement from an area where artemisinin resistance was already present). The presence of partner drug resistance was also assumed. It was assumed that 75 per cent of clinical cases were treated with ACT type 2 (partner medicine: mefloquine) with the remaining 25 per cent being treated with artemisinin monotherapy. The rate of treatment of clinical infections increased in 2005 with the opening of new clinics in the area.
Figure 8: The top graph shows model simulations of the monthly numbers of treated clinical *Plasmodium falciparum* cases (solid blue, left axis) in Mae Sot from 1990 to 2025 with the reported cases (black, left axis) and the predicted percentage artemisinin resistant (dashed red, right axis), partner drug resistant (dashed green, right axis) and ACT resistant (solid red, right axis). The ACT was assumed to be of type 2. The bottom graph shows the expected percentage of infections failing treatment (blue) and the percentage of laboratory confirmed day 42 positive cases from the area.

In order to replicate the rapid rise in treatment failures observed in 2010-12 (Figure 8, bottom graph), an assumption of the probability that a parasite will generate mefloquine resistance is 1 in 10 was required. This effect was less prominent and occurred later if there was a lower rate of influx of artemisinin sensitive infections.

For both Pailin and Mae Sot, only a few simulations that can reproduce the observations are shown here. This is by no means a complete set. However, the simulations serve to demonstrate the following general qualitative results:
1. Artemisinin resistance spreads more rapidly under monotherapy compared to combination therapy

2. ACT using a partner medicine associated with slow mutation of parasites delays the emergence and spread of ACT resistance

3. ACT resistance is more likely to emerge if there are artemisinin resistant infections present

4. The emergence of ACT resistance is likely to be accompanied by an increased rate of treatment failure and possibly followed by increased incidence of clinical malaria.

We reiterate that these model simulations and those in Section 5 are selected to demonstrate potential outcomes if resistance is spreading under a variety of policies, for example no change, switch ACT or containment. We consider small populations where resistance could reach fixation, but do not attempt to model the highly heterogeneous setting of an entire continent where there are so many unknown values, data are not of high enough resolution and the relationship between interacting spatial settings have not been measured. There are model simulations (not shown here) that do not predict the spread of resistance such as in high transmission settings where many infected individuals do not receive treatment because they are immune and do not present with clinical symptoms as well as scenarios in both Pailin and Mae Sot where resistance is not predicted to spread on the timescales represented here.

The model simulations also demonstrate two ways for ACT resistance to emerge. In the Pailin simulations, artemisinin resistance was predicted to emerge under artemisinin monotherapy and then to evolve into ACT resistance. The Mae Sot simulations demonstrate a more worrying mechanism. To mimic the effects of population movement, a constant influx of artemisinin resistance is included. This results in the rapid evolution of ACT resistance. The Mae Sot simulation demonstrates a potential mechanism for artemisinin resistance to spread and lead rapidly to the failure of ACT.
5. The cost and effectiveness of containment

The transmission dynamic mathematical model was extended to predict the cost of various control strategies, the number of disability adjusted life years (DALYs), and the years until less than 0.01 per cent of the population are infected (i.e. the reduction of the \( P. falciparum \) parasite rate (PfPR) to below 0.01 per cent).\(^{28}\) A range of interventions were explored, and their combinations at different coverage levels, to identify the optimal strategy to achieve local elimination of all \( P. falciparum \) malaria within a pre-specified timeframe, set initially as between the present and 2025. This is done in two scenarios of pre-existing low and medium transmission settings, each with a population of 1 million, a constant low influx of artemisinin resistant infection, a baseline coverage of ITNs of 40 per cent at a protective efficacy of 20 per cent, and no use of mass drug administration (MDA), mass screening and treatment (MSAT), primaquine, or a vaccine. The aim here is to provide a qualitative and comparative overview of the cost and effectiveness of different strategies. Their cost-effectiveness in practice will vary widely by context and in response to unit costs of the specific products used.

Two scenarios were considered which are both predicted to have ACT resistance at 50 per cent by 2025 if no further action is taken:
- low transmission and 30 per cent coverage with type 2 ACT
- intermediate transmission and 80 per cent coverage with type 2 ACT.

Various combinations of the following interventions were used to form independent strategies:
- switching ACT from type 2 to type 3
- increasing coverage of ACT treatment of clinical malaria to 80 per cent
- adding a single dose of primaquine to all ACT treatments with the effect of reducing the infectious period of treated infections by 12.5 days\(^{29}\)
- increasing ITN coverage to 80 per cent
- mass vaccination once per year for five years with a coverage of 80 per cent
- MDA using ACT once per year for five years with a coverage of 80 per cent
- MSAT once per year for five years using an RDT with a sensitivity of 80 per cent with a coverage of 80 per cent.

Having identified strategies that are able to locally eliminate malaria in this context and timeframe, their costs and DALYs which are both discounted at a standard rate of 5 per cent were compared.

Figure 9 illustrates the reduction in the number of clinical cases for the baseline scenario and three interventions in an intermediate transmission setting. In the absence of any intervention the


number of cases gradually increases due to the continued spread of resistance to both the artemisinin and the partner medicine. By switching to an alternative ACT which does not face high resistance to the partner medicine, some reduction is seen in the number of clinical cases. By adding MDA to this strategy elimination becomes feasible in approximately eight years, which is reduced to under six years with the further addition of primaquine to both routine treatment of clinical cases and to the MDA program.

Figure 9: Monthly reported cases under four containment strategies

The costs, DALYs and time to the elimination approximating threshold for a range of interventions, individually and in combination, are summarised in Table 2. Switching the pre-existing ACT to one with a different partner medicine is a prerequisite to achieving local elimination. The only exception to this finding is the vaccine, which could achieve elimination were it to be deployed in coming years, even in the presence of resistance to both the artemisinin and the partner medicine.

Table 2: The costs, DALYs and years to the elimination threshold. Where years to the elimination threshold are not stated this indicates the threshold was not reached before 2025. RX60% - increased coverage to a level of 60%. ITN80% - increased coverage of ITNs to 80%.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Low transmission with low ACT rates</th>
<th>Intermediate transmission with high ACT rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cost</td>
<td>DALYs</td>
</tr>
<tr>
<td>Baseline</td>
<td>1 739 530</td>
<td>8 523</td>
</tr>
<tr>
<td>Switch</td>
<td>2 143 880</td>
<td>7 792</td>
</tr>
<tr>
<td>Switch+RX60%</td>
<td>3 563 870</td>
<td>2 767</td>
</tr>
<tr>
<td>Switch+ITN80%</td>
<td>3 837 000</td>
<td>4 253</td>
</tr>
<tr>
<td>Switch+RX60%+PQ</td>
<td>3 558 200</td>
<td>2 258</td>
</tr>
<tr>
<td>Switch+RX60%+PQ+ITN80%</td>
<td>6 685 300</td>
<td>1 703</td>
</tr>
<tr>
<td>Switch+vaccine</td>
<td>17 782 800</td>
<td>1 111</td>
</tr>
<tr>
<td>Switch+RX60%+MSAT</td>
<td>3 284 770</td>
<td>2 324</td>
</tr>
<tr>
<td>Switch+RX60%+PQ+MSAT</td>
<td>3 569 040</td>
<td>1 579</td>
</tr>
<tr>
<td>Switch+RX60%+MDA</td>
<td>21 666 300</td>
<td>1 033</td>
</tr>
<tr>
<td>Switch+RX60%+PQ+MDA</td>
<td>23 678 100</td>
<td>755</td>
</tr>
</tbody>
</table>
In the low transmission setting the interventions are all costlier than the baseline due to the relatively low number of clinical cases. In the intermediate transmission setting all strategies initially face higher costs followed by rapid cost savings and DALYs averted, even in the absence of successful elimination. Elimination is only achieved with the use of a vaccine or with MDA, with the addition of primaquine substantially decreasing the number of years this would take, at a moderate increase in costs.

In the low transmission setting elimination could still be achieved using ITNs alone within a 10 year timeframe while accumulating more DALYs than other strategies. If combined with other interventions, the ITNs would facilitate elimination by effectively reducing the number of required years.

Primaquine was highly effective in the model in lowering the time to elimination and the DALYs, particularly if implemented in both routine treatment of clinical cases and in MDA programs, where elimination in the low transmission model would be achieved in two years. The relatively low dose required for an effective transmission blocking effect is believed to be safe for all individuals. The predicted effect of using primaquine is a conservative estimate since the model does not account for the loss of the artemisinin effect on infectivity in individuals with resistant infections. It is noted, of course, that empirical evidence of primaquine’s impact on transmission has not yet been found.

**Cost-effectiveness**

In the static analysis in Section 3 the large potential costs associated with ACT resistance were shown. Even without accounting for these more speculative costs, most containment measures are likely to be cost-effective due to their direct benefits in lowering the number of malaria cases and eventual elimination in the local area. This is shown in Figure 10 for the intermediate transmission setting, indicating that even in the most costly intervention (MDA with an ACT combined with a single dose of primaquine) the incremental gains would justify the higher expenditure. A vaccine, if available, would be the most cost-effective intervention with an incremental cost-effectiveness ratio of under US$90. For the low transmission area most interventions were cost-effective when assessed against the baseline, although the incremental gains of MDA+primaquine as compared with the next most effective intervention, the vaccine if available or MSAT+primaquine, were not found to be justified. The threshold used for willingness to pay per DALY averted was US$1000, below the current average GDP per capita for SSA.30

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In summary, the analysis indicates that in a model country with a population living in either low or intermediate transmission settings elimination could be feasible using a range of containment interventions. Ultimately the cost-effectiveness values will vary widely by local context, however, this analysis suggests that interventions that are able to eliminate in the shortest time span could be economically justified irrespective of their relatively high costs, and even when accounting only for the direct health gains of the local population. For the low transmission area where elimination is feasible with a wider range of interventions, the most costly options are not cost-effective as compared with the cheaper ones which are also able to eliminate rapidly.
6. Future Mathematical Modelling Work

There are several important research questions which urgently need to be answered to improve our chances of containing resistance. These include development of new tools (medicines, diagnostics and prevention), testing surveillance strategies and behavioural research. This section focuses only on the plans and needs for future mathematical modelling work.

The results presented for the modelling of cost-effectiveness of containment here are general comparisons of interventions and their likely cost-effectiveness for a few scenarios where containment may be deployed. Ideally, once a region has been targeted for containment, a detailed model tailored to that specific region should be developed. These models are extremely complex and require large datasets (see Annex 4). The benefit is that they can be used in the detailed design and planning of containment strategy.

Research goal: country specific models for the detailed design of containment strategy should be developed. There is one under development in Bangkok for Cambodia (already in use), Thailand (planned for 2012) and Lao PDR (planned for 2012).

In some simulations using an intermediate transmission setting and high coverage of ACT routine treatment, the model predicted the spread of resistance regardless of the choice of ACT without a reduction in cases over time. This was the case for scenario 2 in the containment cost-effectiveness model above. Switching early to an alternative ACT would delay the spread of ACT resistance with limited returns since at each switch resistance to artemisinin (both singly and to each ACT) would continue to increase slowly and without a high fitness cost, any ACT resistance that emerged during previous cycles would remain with a risk that any switching back would result in a rapid increase of ACT resistance. This type of cycling is one method of MFT although these models to date have not been used to model a scenario where resistance to the components of the ACT are already present.31

Research goal: the effect of the presence of artemisinin and other single drug resistance should be incorporated into multiple first line therapy models to fully assess the potential of this intervention for containment.

High transmission settings also present unique challenges for modelling the emergence and spread of resistance. Super-infection, recombination and the effect of medicines on multi-clonal infections with different resistance profiles must be developed in order to search for scenarios where resistance might spread in high transmission settings especially if there is an influx of artemisinin resistant infections.32

Research goal: models for artemisinin resistance specifically for high transmission settings must be developed to carefully determine the transmission, resistance prevalence and treatment coverage conditions that are conducive for the emergence and spread of ACT resistance.

Artemisinin resistance is currently characterised by an extended rate of clearance of asexual parasites from the blood during treatment. There has been modelling analysis performed to characterise the most likely biological mechanism underlying this observation.\textsuperscript{33} There has been statistical analysis of the shape of the parasite decay of time and how such time series can be used to obtain a single value to represent the clearance rate in individual patients (clearance half-life).\textsuperscript{34} However, a method for estimating the percentage of resistant infections at the population level is still not available since the current definition of resistance requires frequent parasite counts within patients and even when such data are available, the definition is noisy. If containment strategies are to be triggered based on suspected levels of resistance increasing above a given threshold, then some way of estimating the population level of resistance must be developed. Details of some preliminary work towards this goal can be found in Annex 1, but much more work and data are required to solve this problem.

Research goal: collaborative research on characterising the resistance phenotype and measuring artemisinin resistance must be strengthened.

Including every monotherapy and combination therapy available is beyond the scope of this project, but it is important to consider all the interactions between medicine use and resistance spread. Atovaquone-proguanil is an alternative first line therapy which has a high mutation rate and is being deployed as a monotherapy in some settings. It is important to extend the model to determine the optimal use of this medicine in a multi-drug resistance setting. It has been shown that for ACTs and artemisinin monotherapy (in the Pailin example) that when medicines are used as monotherapies as well as in combination either sequentially or simultaneously in a population the potential for the emergence and spread of multi-drug resistance is increased.

Research goal: models must be extended to include multiple monotherapies including the full range of partner medicines and atovaquone-proguanil.

Substandard or fake ACT is considered to be a real threat to the spread of artemisinin resistance. More research is required into this problem where models will be merged with data on the failure rates in sensitive and resistant infections associated with these products.

Research goal: models must incorporate the use of sub-standard and fake ACTs.

Previous modelling work has indicated that mass vaccination may be a useful component in elimination strategies.\textsuperscript{35,36,37} More exploration of the potential of malaria vaccines incorporating information from all the vaccine trials is required.

Research goal: mass vaccination should be fully explored using data from the vaccine trials and combining results from within-host models with transmission models.

\textsuperscript{36} White, L. J., et al., ‘The role of simple mathematical models in malaria elimination strategy design’, Malaria Journal, 8 (2009), 212.
Since the presence of artemisinin resistance has increased the likelihood that ACT resistance will emerge and spread, it is important to explore fully the mechanism responsible for this increased likelihood. For ACT the partner medicine is present as a monotherapy for an extended period of time after the artemisinin component has decayed in the blood of the patient. This period of partner medicine monotherapy is a weakness of ACT which could be approached by the inclusion of a second partner medicine. Two partner medicines instead of one could be chosen to be matched for half-lives and also in some cases may have the additional advantage of selecting for complementary resistance mutations (e.g. amodiaquine and lumefantrine select distinct alleles of the *Plasmodium falciparum mdr1* gene).38

Research goal: future potential combinations treatment target product profiles should be fully explored such as the combination of artemisinin with two partner medicines which are matched to each other in terms of their pharmacokinetics and the complementary resistance mutations in the parasite.

The dynamic cost-effectiveness model presented here is very preliminary and does not include costs for ongoing surveillance and other program costs in detail. These and other costs are also highly likely to be different for different countries.

Research goal: include surveillance and other program costs in the containment cost-effectiveness model and extend it to be country-specific.

Annex 1: Characterising and measuring artemisinin resistance

Artemisinin resistance is currently characterised by an extended rate of clearance of asexual parasites from the blood during treatment. There has been modelling analysis performed to characterise the most likely biological mechanism underlying this observation. There has been statistical analysis of the shape of the parasite decay of time and how such time series can be used to obtain a single value to represent the clearance rate in individual patients (clearance half-life). A method for estimating the percentage of resistant infections at the population level is still not available. If containment strategies are to be triggered based on suspected levels of resistance increasing above a given threshold, then some way of estimating the population level of resistance must be developed.

We propose two approaches to meet this challenge:

- A statistical approach to characterise the changing distribution of clearance half-lives during the emergence, spread and fixation phases of artemisinin resistance. This type of analysis can be applied to half-lives derived from a given location to search for evidence of the presence of artemisinin resistance and to predict the expected level of the resistance at the time of sampling.

- A statistical approach using a dataset comprising the percentage of day 3 clearers, the distribution of initial parasitaemia and the sample size for a given study population combined with the results of the characterisation of resistant and sensitive clearance half-life distribution as described above.

Clearance half-life model

Our hypothesis is that at any given location there will be a proportion, p, of resistant infections mixed with a proportion, 1-p, of sensitive infections. The distribution of clearance half-lives would be the combination of two distributions: the distribution for the sensitive infections and the distribution for the resistant infections. Between locations, we would expect the proportion of resistant infections to vary, but the distribution of sensitive half-lives to be similar. The distribution of resistant infections may vary depending on the stage of emergence of resistance in the location (early emergence, spread and fixation).

---

We use sets of individual patient half-life estimates from data from two locations: Pailin, Western Cambodia (2007 to 2010); Mae Sot, Western Thailand (2001 to 2011). The locations are stratified by year in order to explore variations in time.

**Observed**

- **No resistance**
- **Emergence**
- **Pre-fixation**
- **Fixation**

**Hypothesised**

**Mae Sot**

\[
y = 0.3404x - 678.68 \\
R^2 = 0.5846
\]

\[
y = 0.0869x - 171.44 \\
R^2 = 0.4027
\]
The estimated mean half-life for the sensitive parasites appears to be consistent for every location and year with a mean of 2.9 and a standard deviation of 0.7. The estimated standard deviation of the sensitive half-lives in each year and location is quite variable with a mean of 0.3 and a standard deviation of 0.2.

In both locations there appears to be a trend for increased values for estimates of the mean resistant half-life over time.

If the resistant mean half-life estimate is statistically different from the sensitive mean half-life, we conclude that there are indeed two distinct distributions and that resistance is present. This is the case in Pailin (2007 to 2010) and in Mae Sot (2005 and 2009 to 2011). In these cases the estimates of the mean of the resistance half-lives (mean=6.2, sd=1) are more variable than that estimated for the sensitive infections.

The estimated mean half-life for resistant infections does not seem to correlate with the estimated percentage resistant.

However, with only eight locations and years, we cannot infer either the existence or non-existence of a relationship.

Where the estimate of the resistant mean is statistically different from that of the sensitive mean we plot the predicted proportion resistant.

Estimates for the percentage resistant in Pailin are consistently high from 2007 to 2010. The percentage resistant, where it can be estimated using this method for Mae Sot, appears to be high in 2005 and then lower but increasing from 2009 to 2011.
Three day clearer model

There is still no genotype for artemisinin resistance. The phenotype is slow clearance, but this is noisy and has many interacting factors. The best definition uses six-hourly measures of parasitaemia and considers the half-life of the parasite load rather than just the clearance time. This is less noisy than the more ubiquitous definition which uses the percentage of individuals still with parasites after three days (daily measures). However, in most locations, parasitaemia is only measured once per day. This approach uses a statistical simulation model based on the distributions of half-lives for the best defined samples of resistant and sensitive populations combined with initial parasitaemia and sample size to determine the most likely underlying percentage of resistant infections in a sample of patients where the only information available is: the sample size; the distribution of parasitaemia on admission; the percentage of individuals still positive on day 3.

---

**Data used to construct the model**

- Derived from mixture model of data from Cambodia and Thailand
  - Distribution of sensitive half-lives ($D_{hs}$)
    - mean
    - standard deviation
  - Distribution of resistant half-lives ($D_{hr}$)
    - mean
    - standard deviation
- Derived from Flegg’s analysis of six-hourly measures data\(^\text{42}\)
  - Distribution of lag times before log-linear decay ($D_{lag}$)
    - mean
    - standard deviation
- Assumption
  - Distribution of expected day 3 measure timing in hours ($D_{3d}$)
    - mean
    - standard deviation
  - Detection limit for reading a positive slide $\delta$

**Data required for a given sample**

- Distribution of initial parasiteamia ($D_{ip}$)
  - mean
  - standard deviation
- Sample size
- Percentage still parasitaemic on day 3

**Model algorithm**

1. Create a range of percentage resistant input values $[p]$
2. For each value of $p$ sample:
   a. $N$ initial parasitaemias from $D_{ip} [\psi]$
   b. $\left(\frac{pN}{100}\right)$ resistant half-lives from $D_{hr} [\eta]$
   c. $\left(\frac{N-pN}{100}\right)$ sensitive half-lives from $D_{hs} [\eta]$
   d. $N$ lags from $D_{lag} [\lambda]$
   e. Timing of day 3 measure from $D_{3d} [\kappa]$
   f. Then time to clear, $\tau$, for each of the $N$ simulations for each value of $p$ is given by:

\[
\tau = \frac{\eta h \left(\phi \nu \right) - h \left(\phi \delta \right)}{h \left(\phi \tau \right)} + \lambda
\]

   g. If $\tau \geq \kappa$ then count as a simulated day 3
   h. Calculate the expected percentage of day 3 clearers for each of the $N$ samples
   i. Calculate the 2.5, 50 and 97.5 percentiles
3. Perform a linear regression for each of $2i$
4. Infer from $3$, the median and 95 per cent ci prediction for the expected percentage truly resistant for the measured percentage still positive at day 3.

\[^{42}\text{Flegg, J. A., et al., 'Standardizing the measurement of parasite clearance in falciparum malaria: the parasite clearance estimator',}
\textit{Malaria Journal}, 10 (2011), 339.\]
The graph below shows how the model estimates of the percentage truly resistant compare to the percentage positive on day 3 for samples from Mae Sot between 1991 and 2011. Two groupings were used: patients with a normal range of initial parasitaemia and those admitted with hyper-parasitaemia.

As can be seen from the graph above, although the two groups (normal and hyper) have quite different percentages of individuals positive on day 3 from the years 2001 to 2005, the 3-day model predictions for the expected percentage resistant overlap for those years.

For the hyper-parasitaemic patients, the half-lives had also been estimated using the model in Flegg. The green squares represent non-zero estimated of the percentage resistant using the mixture model applied to the distributions of half-lives.

In 2005, the mixture model estimated a mean half-life for resistant parasites that was significantly different from the mean of the sensitive half-life distribution. However, it was much lower (4.1 days) than the other estimated mean half-lives of resistant infections.

Although this is a noisy phenotype, either or both methods could be used as an early warning system for the presence of resistance in new locations. The lower limit of the 95 per cent confidence interval being greater than zero is one possible approach for giving a binary result (resistance present yes/no). However, there is relatively poor agreement between the two methods for the point estimates of the percentage of resistance.

This methodology could easily be recoded in R and included in the World-wide antimalarial resistance network (WWARN) suite of online tools as an early warning system of for potential emergence of resistance.

We propose two methods for estimating the percentage of resistant parasites each using a different grade of data:

The 3-day model approach is less robust but requires only the distribution of initial parasitaemia and the percentage positive on day 3. It would therefore lend itself to early stage preliminary scanning of all routinely collected ACT treatment data to prioritise more involved studies.

The mixture model approach is more robust but requires less commonly collected 6-hourly measures of parasitaemia within patients. It would therefore lend itself as a tool for analysing the data collected from specifically designed studies to search for evidence of artemisinin resistance.

In the absence of a universally accepted molecular marker, these approaches at least provide a semi-quantitative approach to estimating the percentage of artemisinin resistance whilst also accounting for the huge levels of uncertainty associated with these estimates. The benefit of integrating this approach with the data collection and curating carried out by WWARN is that as more data become available, this method will allow improved characterisation of the resistance phenotype, uncertainty will be reduced and estimates for all locations will be improved.
Annex 2: Methods and parameter table for the static analysis

Methods

We consider the implications of artemisinin based treatments reaching similar failure rates to previous first line treatments, using a baseline estimate of 30 per cent applied to the latest WHO estimates for incidence of probable and confirmed malaria by country.\textsuperscript{44} The number of treatment failure cases is then adjusted to account for the proportion of \textit{P. falciparum} using country specific estimates.\textsuperscript{45} A small proportion of \textit{P. falciparum} cases are then assumed to deteriorate to severe illness, ranging between 3 and 4 per cent, depending on transmission intensity. Some of these are able to access in-patient care, with the probability of doing so ranging from 30 to 90 per cent that is correlated with GDP per capita using a log function.

For patients without access to care we assume a high mortality rate, with a point estimate of 85 per cent by fitting the model to the WHO incidence and mortality data for the years 2000-2010 and a distribution fitted to a range of expert opinions on this topic.\textsuperscript{46,47} For patients who access a health facility we assume that in areas of high transmission intensity management of severe malaria with effective artesunate provides a 22 per cent reduction in mortality over quinine, while in low transmission areas the relative reduction is 34 per cent, as found in the AQUAMAT and SEAQUAMAT studies. The uncertainty surrounding these estimates is modelled using beta distributions parameterised with the study primary data.

By varying key parameters, including the probability of developing severe disease following treatment failure and access to in-patient care, the model was initially set to resemble a period where artemisinin based treatments were not yet widely used and fit the lower estimates for mortality data for 2000 to 2004. These parameter values were then applied to a scenario where ACTs are effective and coverage is at the higher end of current levels (40 per cent of all malaria cases) and severe malaria is treated with artesunate rather than quinine.

The excess mortality due to ACT resistance is then calculated by comparing the model outcome when varying the treatment failure rates from 5 per cent for sensitive infections to 30 per cent in a scenario of ACT resistance, and by switching the mortality rates for in-patient severe malaria from that of artesunate to that of quinine in the resistance scenario, assuming quinine would still be widely accessible in the presence of ACT resistance.

Productivity losses associated with this excess mortality are estimated using country specific GDP per capita for 2007-2010. These are adjusted for projected 3 per cent growth rate, 5 per cent discounting and by regional crude mortality rates.

Productivity losses due to excess morbidity are calculated assuming one and three weeks of lost earnings due to a case of uncomplicated or severe malaria, respectively.

The excess cost of a treatment failure was estimated as the cost of a diagnostic test and a second ACT. The cost of in-patient care for severe malaria was taken from the literature.\textsuperscript{48} ACT coverage rates were taken from the literature and Demographic Health Surveys.\textsuperscript{49,50}

The uncertainty pervading many of these parameters is partly accounted for by probability distributions fitted from either primary data or the literature where possible or from a range of expert opinions. A Monte Carlo simulation was then run to sample from these distributions 500 times and the interquartile range was selected for all outcomes as a plausible range of estimates.

While the static analysis does not explicitly model the changes in transmission following the increased ACT resistance, results are presented for a modified incidence rate reflecting the possible changes in transmission that could accompany or follow the spread of resistance. A sensitivity analysis was also carried out to test the results with a variation of 50 per cent increase and decrease in incidence over the five years.

### Parameter values for economic analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Point estimate</th>
<th>Range</th>
<th>Comments</th>
<th>Source</th>
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<tbody>
<tr>
<td>ACT failure rate</td>
<td>30%</td>
<td>20%-40%</td>
<td>Approximating the mean failure rates for chloroquine, amodiaquine and sulfadoxine pyrimethamine in SSA and Asia over the last decade</td>
<td>Assumption\textsuperscript{51}</td>
</tr>
<tr>
<td>P TF becomes severe – LTI</td>
<td>0.04</td>
<td>Beta(4:96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P TF becomes severe – HTI</td>
<td>0.03</td>
<td>Beta(3,97)</td>
<td>Best fit to WHO incidence/mortality data</td>
<td>World Malaria Report 2011</td>
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<td>Mortality rate for untreated severe malaria - LTI</td>
<td></td>
<td></td>
<td></td>
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<table>
<thead>
<tr>
<th>Parameter</th>
<th>Point estimate</th>
<th>Range</th>
<th>Comments</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Access to care</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any antimalarial for fever</td>
<td>0.5</td>
<td>0.3-0.5</td>
<td></td>
<td><a href="http://www.measuredhs.com52">http://www.measuredhs.com52</a></td>
</tr>
<tr>
<td>Of those accessing an antimalarial, access to an ACT</td>
<td>0.4</td>
<td>0.1 – 1</td>
<td></td>
<td><a href="http://www.measuredhs.com53">http://www.measuredhs.com53</a></td>
</tr>
<tr>
<td>Access to in-patient care</td>
<td></td>
<td>0.3-0.85</td>
<td>Function of country GDP per capita</td>
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</tr>
<tr>
<td><strong>Costs</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>MDA</td>
<td>0.6</td>
<td>Per capita + medicine cost</td>
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<td></td>
</tr>
<tr>
<td>ACT</td>
<td>US$1.2</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>US$0.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-patient care for severe malaria</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discount rate</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Projected GDP growth</td>
<td>3%</td>
<td>Conservative estimate for average growth in SSA and Asia emerging markets</td>
<td>57</td>
<td></td>
</tr>
</tbody>
</table>

Annex 3: Country specific estimates of excess mortality due to ACT resistance, assuming fixed incidence\textsuperscript{58}

\textsuperscript{58} Country classification is based on the WHO regional office divisions.
Excess annual mortality Asia-Pacific and Eastern Mediterranean

Afghanistan
Djibouti
Egypt
Iran
Iraq
Morocco
Oman
Pakistan
Saudi Arabia
Somalia
Sudan
North Sudan
South Sudan
Syria
Yemen
Bangladesh
Bhutan
DPR Korea
India
Malaysia
Laos
China
Cambodia
Timor-Leste
Thailand
Sri Lanka
Nepal
Myanmar
Indonesia
Viet Nam
Vanuatu
Solomon Islands
Republic of Korea
Philippines
Papua New Guinea
Philippines

- 500  1,000  1,500  2,000  2,500  3,000  3,500  4,000  4,500  5,000
Annex 4: Dynamic Transmission Models

1. The transmission sub-model

This is the basic unit describing the natural history of infection. Individuals are born uninfected and without immunity (S), after challenge, they can develop asymptomatic (I_{A0}) infection clinical (I_{C0}) or severe (I_{S0}) malaria. A proportion, p, of individuals develops symptoms (clinical and severe) and of those, a proportion, q, develop severe infection. Individuals recover from asymptomatic and clinical infection at a rate n which is the inverse of the average duration of infection. Severe malaria cases die at a rate \( \alpha \) or recover at a rate \( v_s \). Once recovered, individuals enter a partially immune state (R). From this state, individuals can become infected but the probability of developing clinical or severe malaria is lower (p_R and q_R respectively). If individuals remain unchallenged for a given length of time (1/w), then the re-enter the non-immune state (S). The risk of challenge is dependent on the number of infected individual present a few weeks earlier.
2. The treatment sub-model

To include treatment, additional states must be included in the model:

- \( I_{D0} \) individuals that are undergoing successful treatment with artemisinin medicines.
- \( I_{rp0} \) individuals that have failed treatment and are experiencing a recrudescent infection with some partner medicine present.
- \( I_{r0} \) individuals experiencing a recrudescent infection without any medicines present.
- \( R_p \) immune individuals with partner medicine.
- \( S_p \) non-immune individuals with partner medicine.
The following decision tree illustrates the transitions from the uninfected to infected states are defined based on the coverage of treatment (c), the use of artemisinin monotherapy (before a given year) versus ACT (after the switch) and the risk of recrudescence for given artemisinin mono or combination therapy ($p_{a0}$ and $p_{act0}$ respectively with $r_0=p_{a0}+p_{act0}$).

Individuals undergo re-treatment at a rate $\tau$, and are assumed to fail with the same probability as normal infections.

Treated infections are assumed to be less infectious by a factor that is given by the time between symptoms and infectiousness divided by the sum of time between symptoms and treatment and the average time under treatment to recovery and loss of infectiousness.
3. The resistance sub-model

In order to model the transmission of artemisinin resistant infections, all the states \( I_{A0}, I_{C0}, I_{S0}, I_{DA0}, I_{rp0} \) and \( I_{r0} \) and flows associated with infection are duplicated to represent artemisinin resistant infectious states. A subscript of 0 represents sensitive infectious states and flows and a subscript of 1 represents resistant states and flows.

Resistance is introduced to the system as an initial condition or via a mutation rate. Resistance spreads in two ways:

3.1 The clearance time of asexual stages under treatment with ACT or monotherapy is longer in resistant infections (3 days versus 1 day) making the duration of infectiousness 2 days longer for resistant infections (14 days for resistant infections versus 12 days for sensitive). The additional length is the time taken for gametocytes to be removed from the body.

3.2 Different proportions of infections recrudesce depending on the treatment and the sensitivity of the infection.

3.2.1 ACT treatment of sensitive infections.

3.2.2 ACT treatment of resistant infections.

3.2.3 Artemisinin monotherapy for sensitive infections.

3.2.4 Artemisinin monotherapy for resistant infections.

In one version of the model, resistance to the partner medicine, other medicines, combinations of medicines and different stages of drug resistance are included. This version is too complex for the spatial heterogeneity structure below where resistance is confined only to artemisinin resistance.
4. The spatial heterogeneity and population behaviour sub-model

This model is currently under development and will be applied for detailed strategy design for specific areas where containment is being planned.

The population is divided into $N_p$ interacting geographical subpopulations (patches). For example, a model for Cambodia would have 77 interacting operational districts whereas a model for Pailin would have 116 interacting villages.

Within each patch, the population is divided into a set of population typologies, with each type having a given level of connectivity with the other types. For example, the current structure has three typologies:

4.1 The static population

4.1.1 Modelled as staying within the same patch but able to catch malaria from infected individuals from other patches with a probability inversely proportional to the distance between patches.

4.2 The mobile population

4.2.1 Modelled as well mixed with flows of movement between patches based on the values of an $(N_p \times N_p)$ matrix of flows. This matrix is to be parameterised using information from census surveys and population movement studies.

4.2.2 It is assumed that susceptibility and infectiousness of individuals in this population is higher than in the static population due to lifestyle and accommodation differences.

4.2.3 It is assumed that coverage of interventions will be lower in this population than in the static population.

Each patch will have:

4.4 A given transmission potential inferred from observations of clinical infections.

4.5 A given coverage of presumptive treatment inferred from data on Village Malaria Workers (VMW) and health centre coverage.

4.6 A given effect of ITN, long lasting insecticide treated nets (LLIN) and long lasting insecticide treated hammock nets (LLIHN) inferred from coverage by district or village.

5. Data

5.1 Data from CNM Cambodia

5.1.1 Village code

5.1.2 Village number

5.1.3 Population estimate

5.1.4 X coordinate of village ($X$) [if missing select random sample from uniform distribution with range $X_{HC_{new}}-D_{HC}$ to $X_{HC_{new}}+D_{HC}$]

5.1.5 Y coordinate of village ($Y$) [if missing select $Y=Y_{HC_{new}}\pm(D_{HC}^2-(X_{HC_{new}}-X)^2)^{0.5}$]

5.1.6 HC (health centre) code

5.1.7 Distance from HC in km ($D_{HC}$)

5.1.8 Distance from HC used to get HC coordinates from village coordinates ($D$)

5.1.9 X coordinate estimate of HC ($X_{HC}$) [if $D=0$ then select random sample from uniform distribution with range $X_{HC}-D$ to $X_{HC}+D$ to get $X_{HC_{new}}$ else $X_{HC_{new}}=X_{HC}$]
5.1.10 Y coordinate estimate of HC (YHC) [if \( D \neq 0 \) then select \( YHC_{new} = YHC \pm (D^2 \cdot (XHC - XHC_{new})^2)^{0.5} \) else \( YHC_{new} = YHC \)]

5.1.11 VMW present 2007
5.1.12 VMW present 2008
5.1.13 VMW present 2009
5.1.14 VMW present 2010
5.1.15 Long lasting insecticide nets distributed 2007
5.1.16 Long lasting insecticide nets distributed 2008
5.1.17 Long lasting insecticide nets distributed 2009
5.1.18 Long lasting insecticide nets distributed 2010
5.1.19 Long lasting insecticide hammock nets distributed 2007
5.1.20 Long lasting insecticide hammock nets distributed 2008
5.1.21 Long lasting insecticide hammock nets distributed 2009
5.1.22 Long lasting insecticide hammock nets distributed 2010
5.1.23 Conventional nets distributed 2007
5.1.24 Conventional nets distributed 2008
5.1.25 Conventional nets distributed 2009
5.1.26 Conventional nets distributed 2010
5.1.27 Retreated nets distributed 2007
5.1.28 Retreated nets distributed 2008
5.1.29 Retreated nets distributed 2009
5.1.30 Retreated nets distributed 2010
5.1.31 MSF mobile malaria worker coverage in 2004
5.1.32 MSF mobile malaria worker coverage in 2005
5.1.33 MSF mobile malaria worker coverage in 2006.

6. Incorporation of data into model
6.1 Bednets
An efficacy level and half-life is assigned to each type of net, then the efficacy function of a set of nets of a given type distributed in a given year is given by an exponential decay function with initial condition of maximum efficacy at the year of distribution multiplied by the coverage in that year and a decay rate of \( \ln(2)/\text{half-life} \). Then the reduction in transmission factor is given by the sum of all the efficacy functions capped at the maximum efficacy value subtracted from unity.

6.2 Routine treatment of clinical cases
For each village, in the absence of VMW or Mobile Malaria Worker (MMW) coverage is assumed to be the baseline level. If a VMW or MMW is present then the coverage is given by the estimate of the efficacy of VMW or MMW.

7. Remote villages
Some villages are defined as remote. Remote villages are:
7.1 Located at a long distance from the nearest health centre HC
7.2 Have higher R0 values
7.3 Have lower connectivity with other villages
7.4 Will have lower coverage of components of new intervention strategies.

This is incorporated into the model in the following way:
- A threshold distance from health centre is given as a parameter. Then all villages with a distance greater than the threshold are assigned as remote. The number of remote villages (nrem) is derived.
• A list of basic reproduction numbers are generated using a log-normal distribution of mean and standard deviation as given in the parameter list. Then the highest $r_{rem}$ values are assigned randomly to the remote villages and the remaining values are assigned randomly to the non-remote villages.

• A reduced connectivity factor is given as a parameter. Then the remote-non-remote connectivity values based on geographical distance are multiplied by the factor. The remote-remote connectivity values based on geographical distance are multiplied by the square of the factor.

• A reduced coverage factor is given as a parameter. Then all the components of the integrated elimination strategy for a given simulation will be multiplied by this factor for remote villages.

8. Mobile population

The mobile population in Pailin is modelled as a remote village with zero coverage of current interventions, randomly assigned X-Y coordinates (thus allowing for uncertainty in the connectivity between the mobile population and the static population) and randomly assigned population size.

This could be developed further by considering a growing mobile population or other dynamic characteristics.

9. Elimination strategies

Potential components of a spatially explicit integrated elimination strategy are listed below in ascending order of logistical, economic and ethical acceptability.

9.1 Future distribution of LLIN, LLIHN, Conv, RT nets

9.2 Increasing access to routine treatment of clinical infection (via VMW and other schemes)

9.3 MDA/MSAT with ACT/malarone

9.4 Adding a single dose of primaquine to MDA/MSAT treatments

9.5 Adding a single dose of primaquine to routine treatment of clinical infection.

Thresholds in some measure of transmission (either total cases in the previous year or current prevalence) combined with thresholds in interventions currently deployed (e.g. predicted effective protection levels of nets, presence/absence of a VMW) will be used to trigger the inclusion of each component for each village at a given start time for the elimination strategy. A higher acceptability of a given component will be associated with a higher threshold. A composite elimination strategy for the district will then be automatically designed.

Imperfect execution of the composite elimination strategy will be modelled as individual villages being excluded in random years with a given probability.

10. Strategy design through sensitivity analysis

The model will be run repeatedly for parameter values that are randomly selected from the ranges given above. This should allow for uncertainty in the values of the parameters. For the intervention parameters, values will be randomly selected to conform to specific intervention strategies if switched on. For each run, the values of every parameter will be recorded along with the predicted number of both sensitive and resistant infected individuals. This output will then be analysed to determine the strategy with the greatest likelihood of success and identify parameters to which the system is most sensitive.
References


Maude, R. J., et al., ‘The last man standing is the most resistant: eliminating artemisinin-resistant malaria in Cambodia’, *Malaria Journal*, 8 (2009), 31.


Saget, C. *Fixing Minimum Wage Levels in Developing Countries* (Jakarta: ILO, 2006).


Notes