

# **Consensus modelling evidence to support the design of mass drug administration programmes**

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## Executive summary

- In 2015 the MPAC will consider the evidence for the use of MDA in low transmission settings
- To support this the MMC conducted a model comparison exercise to identify the most important determinants of MDA effectiveness
- A variety of MDA operational considerations were included and their effect in different transmission settings analysed
- The outputs from four models were compared and consensus answers were reached on the following results:
  1. MDA with long-lasting ACTs is predicted to reduce transmission over a much longer timescale than the persistence of the prophylactic effect alone. Percentage reduction in transmission will be higher and last longer at lower baseline transmission levels.
  2. Treating a large proportion of the population in a single year in at least one round is a key determinant of MDA effectiveness whether it is achieved through high coverage in a single round, or reaching new individuals by implementing additional rounds.
  3. MDA will be more effective if conducted in the low transmission season and over longer time periods however the effect of the timing is small relative to other operational factors, if high coverage is achieved
  4. Varying the time interval between rounds from 4 to 6 weeks and the addition of primaquine to MDA with ACTs has little additional impact on transmission, even in the context of artemisinin resistance
- There is a high degree of consensus among the models on the relative influence of the operational factors analysed
- Differences in the predicted impact size arise due to the different assumptions made about malaria transmission in each model which represent realistic uncertainties in our understanding of this process

## Introduction

In September 2015 the Malaria Policy Advisory Committee (MPAC) will review the evidence for the effectiveness of Mass Drug Administration (MDA) in low transmission settings. This will include the use of MDA for long term transmission suppression and elimination purposes as well as its use for epidemic containment and emergency response.

To complement the field trial evidence assembled separately by the Evidence Review Group (ERG) in April 2015, four groups from the Malaria Modelling Consortium (MMC) have conducted the following analysis to identify the consensus results among four established malaria transmission models on the effectiveness of MDA under different operational configurations and in different transmission settings. The analysis was limited to specific requests to address the key issues arising from the ERG and does not necessarily cover all questions on optimal and strategic deployment of MDA which further modelling work could help inform.

Given the large number of different possible combinations between MDA programme options and transmission setting characteristics (Table 1) measuring the effect of MDA effectiveness in each of these combinations using standardised field trials is infeasible and impractical. Instead malaria transmission models can predict what changes we might expect to happen given the field trial results we have already observed. Effectiveness or impact, for the purpose of this analysis is defined as the percentage reduction in annual average *Plasmodium falciparum* parasite rate as measured by PCR ( $PfPR_{PCR}$ ) in individuals of all ages three years after the last year of a given MDA programme.

Mathematical models are a useful way of evaluating the knowledge accumulated from existing MDA field trials. The models on display in this report have all been fitted to the MDA trials data as well as epidemiological data accumulated from malaria studies. While there is no way to guarantee that the mechanisms in these models are correct, or that the differences in the models do not explain the differences in their outcomes, the results of the models are consistent with most of the published data about malaria epidemiology and transmission. Most importantly though, the models may disagree in small ways, but they agree overall about the patterns and likely outcomes of MDA to such an extent that they can be used to support some robust policy recommendations on the use of MDA.

Previous modelling work from different modelling groups has identified some common themes on which factors are most likely to be important for optimising the use of MDA for malaria elimination(1-6). While interpreting these general trends from independent work is valuable, each of these analyses was performed in different epidemiological settings with different assumptions about how MDA is performed and the effect that it has. This hinders any formal comparison of the results derived from the models as we cannot be sure if differences arose due to the different input values of the models, or due to the different assumptions about malaria transmission made by each model. While it is important to standardise inputs and outputs for a formal model comparison, differences in model formulation and validation (see Appendix) represent important uncertainties in our understanding of malaria transmission that should be preserved in any output.

In this model comparison exercise we standardise the inputs and outputs of each of the models to derive directly comparable MDA effectiveness results for the first time. This has the advantage of being able to produce consensus quantitative estimates of effectiveness under different scenarios, whilst incorporating the uncertainty in modelling the malaria transmission process. The aims of this quantitative model comparison are as follows:

## Aims

1. Via a limited number of simulation scenarios of operationally feasible MDA, we aim to estimate the impact of MDA on prevalence in low transmission settings
2. Additionally, this report aims to investigate model consensus on optimal strategies (among the operationally feasible strategies examined) to implement MDA in different low transmission settings

## Methods

These aims are investigated through a series of simulations that analyse the changes in effectiveness of MDA from a baseline scenario in response to changing MDA operational characteristics. The baseline scenario was developed in collaboration with MDA field trial partners to most closely represent the transmission settings and operational constraints of MDA that are reported by the ERG. Parameter values for the baseline scenario are shown in Table 1. The output effectiveness metric for all analyses was the percentage reduction in annual mean  $PfPR_{PCR}$  in the 3<sup>rd</sup> year after the final year in which MDA is implemented (see example output in Figure 1).

**Table 1 Parameters for the baseline scenario.** \* Effective coverage is defined as: the percentage of the population that take the full course of drug which clears all parasites (access to intervention x adherence x drug efficacy). The denominator corresponds to the entire population and those not covered includes those ineligible *e.g.* pregnant women and individuals under 6 months of age

Parameter	Value
Programmatic considerations	
Number of MDA rounds per year	2 rounds
Effective coverage*	70%
Coverage correlation between rounds	1 (same people are treated in each round)
Interval between rounds	5 weeks
Duration of MDA programme	2 years
Time of year MDA begins	Optimal (as defined by each group) in a Zambia-like seasonality
Other interventions	ITNs at 80% effective coverage and access to passive treatment with ACTs at 60%
MDA drug choice	Long-lasting ACT with properties similar to DHA-piperaquine
Addition of low-dose primaquine (0.25mg/kg) to MDA drug	No
Transmission setting characteristics	
Baseline transmission intensity	5% $PfPR_{2-10}$ as measured by microscopy
Importation of malaria cases	None
Population size	10,000 people
Artemisinin resistance	0%
Seasonality profile	Zambia-based single season profile

### *Primaquine analysis*

To investigate the additional impact of adding low dose (0.25mg/kg) primaquine to MDA with long lasting ACTs, two simulations of the baseline scenario were run, one with primaquine and one without. The MORU modelling group also implemented a corresponding analysis, but in the presence of artemisinin resistance.

### *Key operational variables*

Among the fixed variables in the baseline scenario (Table 1) there is a subset of key operational variables that are of primary interest as they can be adjusted in an MDA program. These variables were investigated in a multivariate analysis which simulated the baseline conditions (Table 1) with every combination of the following core variable parameters (giving  $2 \times 4 \times 3 \times 2 = 48$  different scenarios):

1. Number of rounds per year (2 or 3)
2. Effective coverage of each round (30%, 50%, 70% or 90%)
3. Weeks between each round of MDA (4, 5 or 6)
4. Duration of MDA programme (1 or 2 years)

This allowed us to observe the effect of changing any one of these variables, either in isolation, or in combination to test for potential interactions between the variables.

### *Predicted effect in different contexts*

In this analysis we also tested how the effectiveness of a typical MDA programme might vary in different transmission settings. This involved re-running the baseline scenario (Table 1) but changing each for the following variables in isolation (one variable at a time):

1. Seasonal timing of MDA rounds (in settings with 1 or with 2 rainy seasons)
2. Starting *PfPR* in 2-10 year olds as measured by microscopy (0-10%)
3. Imported infections per 10,000 people per year (0, 0.4, 1.6)
4. Population size (1000, 3000, 10000 people)

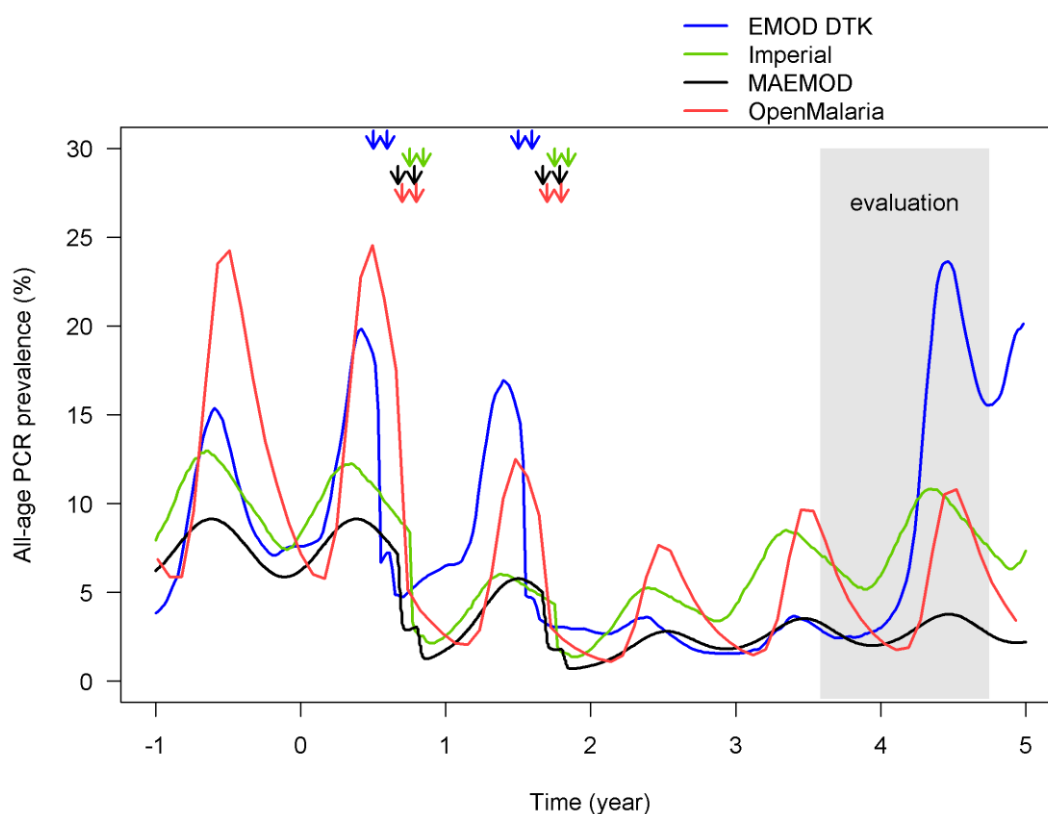
### **Summary of model differences**

The key elements that differ between the models that are likely to impact the outcomes are summarised in the Appendix. The most important structural difference is between the three stochastic model systems (OpenMalaria, EMOD DTK and Imperial) and the MAEMOD deterministic model. Further differences between all the models include the way they represent the relationship between EIR and prevalence, human immunity, super-infection, and clonality of infections. Furthermore the data used to fit and validate the models differ with OpenMalaria, EMOD DTK and Imperial primarily using data from sub-Saharan Africa and MAEMOD using data from the Greater Mekong Sub-region. Only a full harmonisation exercise would dissect the precise cause of differing magnitudes of predictions in MDA impact given by each of the models and this was not carried out due to limited time for the exercise. In this analysis we focus on the consensus results and the relative impact of MDA with different operational characteristics.

## Results

### Example model output

Simulations of the baseline MDA scenario and its impact on all-age  $PfPR_{PCR}$  from each of the four models is shown over time in Figure 1. Immediately following MDA there is a dramatic drop in prevalence due to successful cure of infection and the prophylactic effect of ACTs with a long half life. However in the absence of elimination, the prevalence of infection is predicted to return to pre-intervention levels (albeit at different rates depending on the model), a feature termed resilience in malaria transmission models. The reason for this is that the key factors which determine local transmission intensity and therefore prevalence of infection are the local density of mosquitoes, their rate of biting humans, and the rate at which infected humans clear parasitaemia. Once inhibitory blood drug levels decline in those participating in the MDA, none of these factors have been changed permanently, and thus transmission will re-establish at pre-MDA levels. Without some other change, such as improved vector control, the effects of MDA are likely to be transient.



**Figure 1** Example simulated output from three different models

The timing of each MDA round in each model is shown by coloured arrows. The four different models show the output under the baseline scenario (coverage = 70%, 2 years of MDA, 2 rounds per year, 5 weeks between rounds, seasonal transmission (based on Zambia), mean annual prevalence pre-intervention by microscopy in 2-10 year olds ( $PfPR_{2-10}$ ) = 5%).

### Size of MDA impact: model comparison

While the four different models all show similar trends in the impact of MDA over time (Figure 1), in terms of an initial rapid reduction in  $PfPR_{PCR}$  followed by a rebound in transmission, substantial differences can be observed in both pre-intervention transmission and the predicted magnitude of MDA impact in the baseline scenario (Figures 1 and 2). EMOD DTK and MAEMOD

predict the largest % reduction in  $PfPR_{PCR}$  of 64%, OpenMalaria the next largest at 58% reduction, and Imperial the smallest at 19% reduction.

There are many differences in assumptions between the models which cause the differences in resilience shown in Figure 1, for example, the pre-intervention PCR prevalence which is determined by the assumed relationship between slide-prevalence and PCR prevalence, the relationship between EIR, prevalence and the basic case reproduction number ( $R_0$ ), the assumed degree of heterogeneity in exposure of the population to mosquito bites, the impact of ongoing case management, the degree of stochastic variability in the model and the dynamics of immunity (see Appendix and the Discussion for more details on model assumptions). We did not undertake a formal analysis to quantify the absolute or relative impact of these assumptions on the outcomes due to time constraints.

There are many differences in assumptions between the models which could cause these differences and these are listed in the Appendix as well as in the discussion section. Despite these differences between the size of impact predicted by the different models, we found generally greater agreement as to the relative impact of different operational characteristics of MDA in different transmission settings. These findings are detailed below.

	2 rounds, 1 year				3 rounds, 1 year				2 rounds, 2 years				3 rounds, 2 years			
	EMOD DTK	Imperial	MAEMOD	OpenMalaria	EMOD DTK	Imperial	MAEMOD	OpenMalaria	EMOD DTK	Imperial	MAEMOD	OpenMalaria	EMOD DTK	Imperial	MAEMOD	OpenMalaria
90%	48	25	50	59	57	33	85	58	88	42	97	83	98	56	100	80
70%	14	16	24	35	28	16	48	38	64	19	64	58	72	21	95	60
50%	3	7	12	22	15	7	23	28	41	11	28	30	60	11	58	37
30%	2	4	6	15	19	4	10	15	30	10	11	19	19	8	20	22

**Figure 2** Percentage reduction in mean annual all-age PCR prevalence ( $PfPR_{PCR}$ ) in 3rd year after the intervention has ended. Darker colours indicate larger reductions.

## Programmatic factors

### Effective coverage

Effective coverage has a large impact on  $PfPR_{PCR}$  percentage reduction in all the models. For example, the median estimated % reduction in  $PfPR_{PCR}$  3 years after 2 rounds of MDA within a year spaced 5 weeks apart at 30% coverage is 5% (range across models 2-15%), while the median impact at 70% coverage is 20% reduction (range 14-35%) (Figure 2).

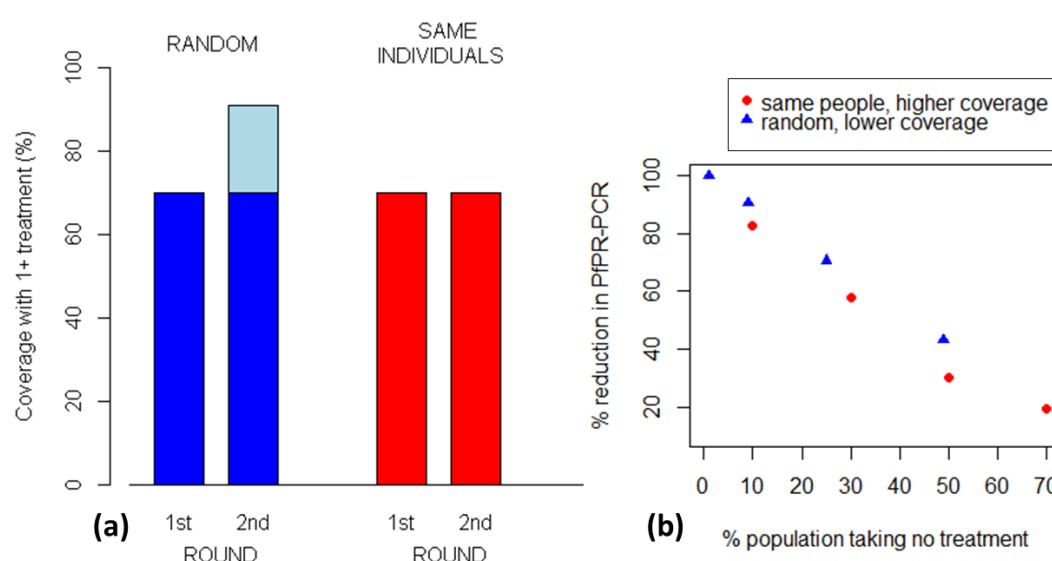
### Overlap in coverage between rounds

When multiple rounds of MDA are carried out, all the models show that coverage overlap (whether the same or different individuals participate in each round) has a significant impact on MDA effectiveness due to its direct influence on overall effective coverage. For example, if participation was entirely random in each round, 2 rounds of MDA at 70% coverage would mean that approximately 90% of the population would receive one or more treatment courses. At the other extreme, however, if exactly the same individuals participated in each round, then 2 rounds at 70% coverage would still only reach 70% of the population (Figure 3a). In reality, the situation is likely to be somewhere between the two extremes.



The models indicate that, with closely-spaced rounds of treatment (such as the 4-6 week intervals considered in the scenarios here), the most important operational factor determining MDA impact is the proportion of the population who do not receive any MDA treatment in any rounds (Figure 3b). This can be reduced by either high per-round coverage or through reaching different individuals in additional MDA rounds in the same year. Figure 3b shows the close relationship between the proportion of the population not receiving treatment in any round, and MDA impact in the OpenMalaria model. This relationship was examined in the EMOD DTK and Imperial models and the same conclusions were drawn (results not shown).

Coverage overlap in MDA rounds with a long gap between them (e.g. 2 years of MDA with 1 round per year) is predicted to be less important for MDA impact. This is because sufficient time has elapsed for many individuals taking part in the first round of MDA to become reinfected (assuming transmission is not extremely low or interrupted in year 1). As prevalence declines, however, the models suggest coverage overlap in different years may become more important, especially in longer MDA programmes.



**Figure 3** Overlap in coverage between MDA rounds and impact on PfPR-PCR. (a)

The proportion of the population receiving 1 or more treatment courses after 2 rounds of MDA, each at 70% coverage with either random participation or the same individuals participating each time. (b) % reduction in  $PfPR_{PCR}$  3 years after MDA according to the % population not receiving treatment in any rounds in the baseline scenario. Blue dots represent two rounds of MDA randomly targeted at 30%, 50%, 70% and 90% coverage while red dots represent the same two rounds of MDA but where the same individuals are treated each round. Results shown are from the OpenMalaria model.

### Number of rounds

The impact of 2 versus 3 rounds per year depends on what extent the additional round reaches individuals not covered in the first round, as described above. If exactly the same individuals participated in each round of MDA, as assumed in the EMOD DTK, Imperial and OpenMalaria baseline simulations, having a third round made negligible difference to the outcome in any of the models when the rounds were spaced 4-6 weeks apart (Figure 2). If the people treated in each round were a random selection, as in the MAEMOD model, then the efficacy of 3 annual rounds was greater than that of 2 rounds in all scenarios (Figure 2 and 3).

### Interval between rounds

In all the models, there was minimal difference in MDA impact when within-year MDA rounds were spaced 4, 5 or 6 weeks apart (Figure A1, Appendix). The Imperial, MAEMOD and

OpenMalaria models estimated that in the scenario with 3 rounds of MDA per year for 1 year at 70% coverage and 5% pre-intervention  $PfPR_{2-10}$ , the median % reduction in  $PfPR_{PCR}$  3 years later was 36% (range 12-47%) with 4-week spacing and 37% (20-47%) with 6 week spacing. The same result was found across every transmission setting examined in this exercise (baseline  $PfPR_{2-10}$  1%, 5% or 10%, and in seasonal and non-seasonal settings). The insensitivity of the results to these changes in spacing is due to the fact that reinfection rates between rounds are low over the course of 4-6 weeks, because of the low transmission and long post-treatment prophylaxis in the scenarios considered here.

### **Duration of intervention**

Prevalence remains lower for a longer period with a 2-year MDA campaign than a 1 year MDA campaign. Based on  $PfPR_{PCR}$  outcomes 3 years after the end of the *last round* of MDA, all the models found some greater impact of a longer duration of MDA (Figure 2). In the baseline scenario, there was a median % reduction in  $PfPR_{PCR}$  of 61% (range 19-64%) after 2 years of MDA and 20% (14-35%) after 1 year.

### **Addition of Primaquine to ACT MDA**

The four models are, in most scenarios, aligned that adding primaquine to an ACT only increases the MDA impact further by a small amount. The reduction in  $PfPR_{PCR}$  was increased by a range of <1% to 8% in the MAEMOD and Imperial models, in agreement with previous OpenMalaria modelling results for southern Zambia, which found this intervention had negligible effect (7). EMOD DTK, however, did find in previous work in higher transmission settings that primaquine added to artemether-lumefantrine increased relative impact on  $PfPR_{PCR}$  by a modest 13% and could increase the impact by up to 50-60% when added to DHA-piperaquine (5).

The generally low impact predicted in the models is because, in the data used to parameterize the models, ACTs are already so effective at preventing onward transmission without primaquine that, in the simulations, most transmission after the MDA has ended arises from those who did not participate in the MDA, not from those who were treated. However, the EMOD DTK model found a greater effect of DHA-piperaquine + primaquine because the combination of a long-acting and a highly gametocytocidal drug meant that a proportion of the population was effectively stopped from participating in transmission for a period of weeks. The other models did not find this, and was likely due to different assumptions about how effective DHA-piperaquine is at preventing onward transmission without primaquine.

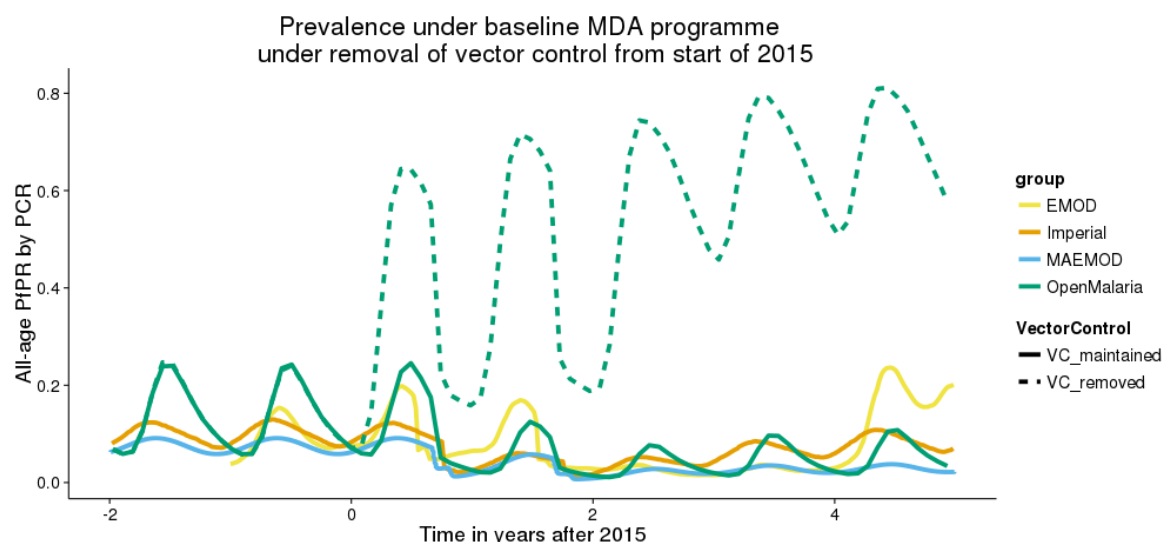
These results are based on data from areas with artemisinin-sensitive parasites. Previous modelling by MAEMOD has shown that primaquine has a slightly greater additional effect in the presence of artemisinin resistance (8). For example, when 0% of infections are artemisinin-resistant, MAEMOD estimates that adding primaquine to an ACT in an MDA done at 70% coverage will increase the reduction in  $PfPR_{PCR}$  by 5%, and when 10% of infections are artemisinin-resistant, primaquine increases the reduction to 6.2%.

### **Replacing vector control with MDA**

The use of MDA in the context of removal of vector control was explored using the OpenMalaria model. This was modelled as a tenfold increase in the emergence rate of adult mosquitos starting at the beginning of 2015, which is followed by the baseline programme of MDA (coverage = 70%, 2 years of MDA, 2 rounds per year 5 weeks between rounds, seasonal transmission (based on Zambia), mean prevalence pre-intervention by microscopy in 2-10 year olds ( $PfPR_{2-10}$ ) = 5%).

The removal of vector control led to a sudden and large increase in all-age prevalence, and the subsequent MDA programme did very little to reduce this shift even in the short term. We predict, therefore, that an MDA programme of this type is insufficient to totally replace vector

control, even at high levels of coverage. A separate report has been submitted for the September MPAC meeting on simulating the effects of scaling back vector control, which includes a more detailed analysis of replacing vector control with mass screen and treat interventions (9).



**Figure 4 Predicted impact of replacing vector control with MDA**

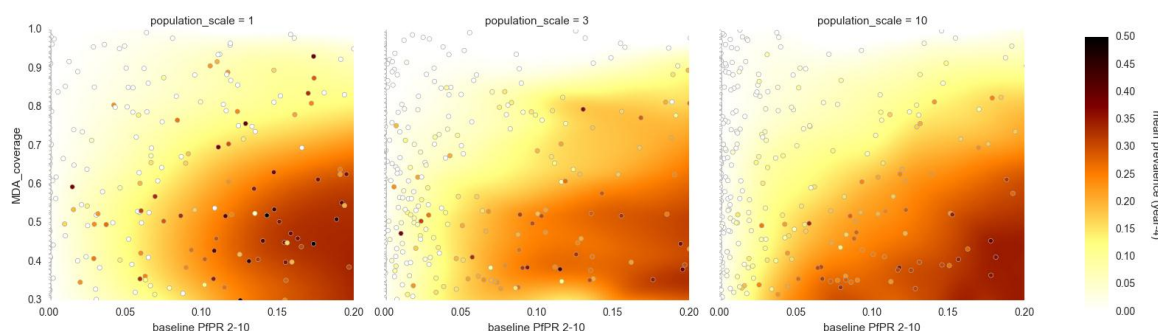
All-age  $PfPR_{PCR}$  prevalence over time. The dashed line shows prevalence in the OpenMalaria model scenario where vector control is removed at the start of 2015 and an MDA programme is begun later that year. For comparison, the unbroken lines show the equivalent scenarios from the OpenMalaria and Imperial models where the same MDA programme is carried out in the context of maintained vector control.

### Setting-dependent factors

#### Baseline transmission intensity

All the models show that the impact of MDA is highly sensitive to the pre-intervention prevalence (Figure 5). Areas of low prevalence will experience a much greater impact (in terms of percentage reduction in prevalence). This is because low transmission settings are less resilient, *i.e.* transmission takes longer to rebound. In a stochastic model framework, all models predict that elimination is possible with MDA in very low prevalence settings ( $\sim 1\%$   $PfPR_{2-10}$ ) in a proportion of simulations.

In a higher prevalence setting ( $10\%$   $PfPR_{2-10}$ ), the percentage reduction in  $PfPR_{PCR}$  is considerably lower than for a setting with 5% prevalence. We predict that even with high coverage (90%), three rounds per year and 2 years of intervention,  $PfPR_{PCR}$  3 years later will only be reduced by a median of 48% (19-95%) from its pre-intervention level, compared to 80% (56-100%) in the setting with 5% baseline prevalence. However, the percentage point reduction in prevalence – *i.e.* the absolute reduction – is greater in higher prevalence settings as more infections are being cleared. In these settings, MDA is less likely to eliminate but will have higher impact on burden if it is part of a long term scaled-up control programme.

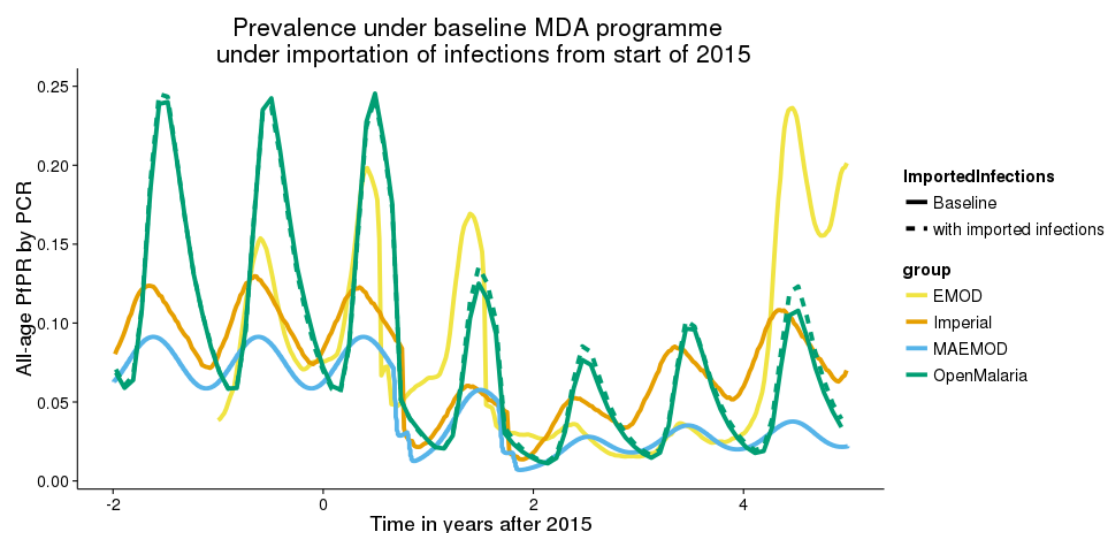


**Figure 5 Impact of MDA in settings with different baseline transmission intensity and population sizes**

The figure presents mean prevalence 3 years after the baseline MDA programme (Table 1) from 100 stochastic simulations in populations of 1,000 (left), 3,000 (middle) and 10,000 (right) individuals. Results shown are from the EMOD DTK model; similar trends were seen in other models.

## Importation

OpenMalaria and EMOD DTK simulated ongoing importation during MDA at rates of 0.4-1.6 infections per 10,000 people per year, based on data from Zanzibar (10). In the baseline scenario of 5% PfPR<sub>2-10</sub>, imported cases occurring at this rate are a very small proportion of the total existing infections in the population, and therefore the results are not sensitive to importation (Figure 6). Our baseline assumption of high access to treatment also means that many imported cases are treated before transmitting onwards. However when PfPR<sub>2-10</sub> is lower, or in a scenario where MDA has eliminated transmission or brought it to a very low level, imported cases would constitute a much larger proportion of cases and would be instrumental to increasing transmission.



**Figure 6 Predicted impact of imported infections**

All-age PfPR<sub>PCR</sub> prevalence over time. The dashed line shows prevalence in the OpenMalaria model scenario where imported infections are introduced at the start of 2015 at the rate of 1.6 infections per 10,000 people per year. The baseline MDA programme is begun later that year at 70% coverage. For comparison, the unbroken lines show the equivalent scenarios from the OpenMalaria and Imperial models where the same MDA programme is carried out with no importation of infections.

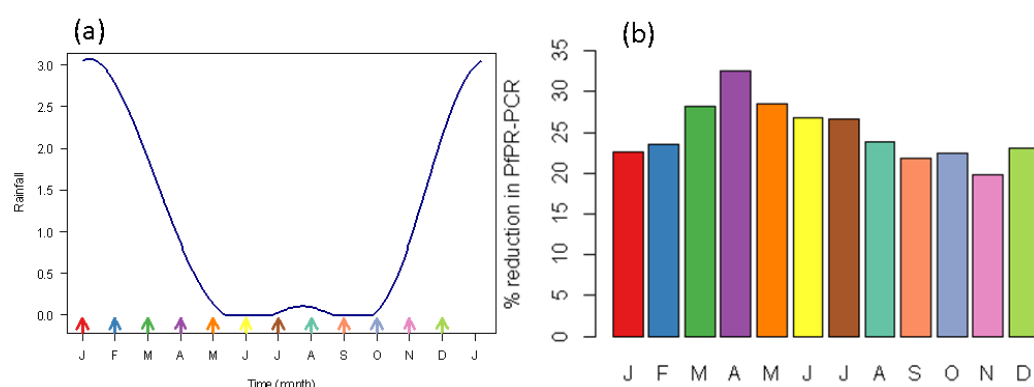
## Population size

MDA more easily causes stochastic extinction in smaller simulated populations, and there is greater simulation-to-simulation variability. Example model output is shown from EMOD DTK (Figure 5). The other stochastic models (OpenMalaria and Imperial) show the same trend in results.

## Optimal timing

Following the findings of other simulation studies (2, 3, 8, 11, 12), we simulated MDA in the dry season to represent optimal timing. With the Imperial model this resulted in lower subsequent prevalence than MDA applied in the wet-season.

In an area with highly seasonal transmission, conducting MDA at the optimal time will increase the effectiveness of the intervention. For example, at 70% coverage the average reduction in  $PfPR_{PCR}$  is estimated by the Imperial model to be approximately 1.45 times larger 3 years after conducting MDA at the end of the rainy season (April) compared to the  $PfPR_{PCR}$  reduction expected after conducting MDA at the beginning of the rainy season (November) (Figure 7). For OpenMalaria, this effect is not as pronounced but is more visible at high coverage. For MAEMOD, the timing affected the magnitude of the initial drop in prevalence immediately following a round of MDA, the optimal timing being halfway between the peak and trough in prevalence, but timing had little effect on the longer term reduction. The optimal time for MDA in a setting with two rainy seasons, such as seen in East Africa, was examined in the Imperial model. Because transmission is more evenly spread over the year in such settings, there is considerably less effect of MDA timing. At a given average baseline slide prevalence level, MDA is predicted to be marginally more effective in a seasonal setting compared to a non-seasonal setting (assuming the MDA is conducted at the optimal time).

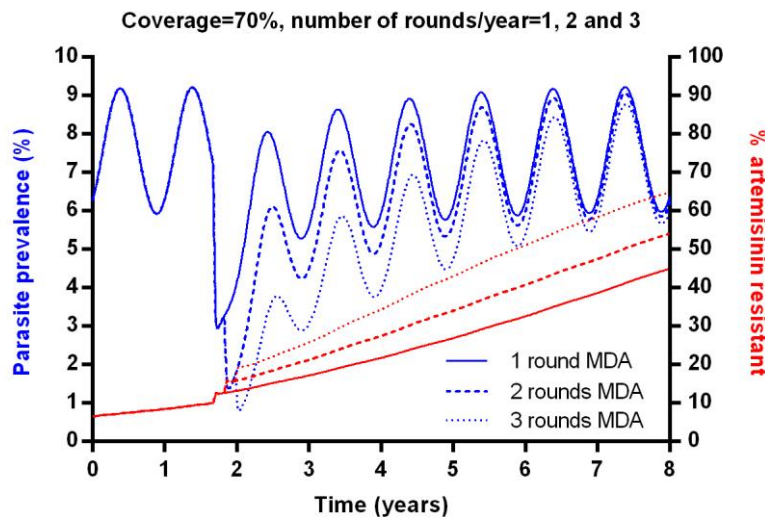


**Figure 7 Optimal timing in the Imperial model**

(a) smoothed annual rainfall pattern (b) % reduction in  $PfPR_{PCR}$  from baselines.

## Artemisinin resistance

MAEMOD has been used to simulate ACT-based MDA in the presence of artemisinin resistance. These results indicate that MDA to some extent speeds up the selection of resistant strains (Figure 8), but this effect is not very large because there is already a significant selection pressure from the case management of symptomatic cases.



**Figure 8** Impact of MDA with ACT on malaria prevalence and the % of artemisinin resistant parasites

## Discussion

While individual models may show different magnitudes of overall impact, there is substantial consensus among the models on which factors have the greatest influence on impact, including both the characteristics of the MDA program and the transmission setting in which it is applied.

Percentage reductions are highest with low transmission settings, longer duration programmes and low simulated population sizes. Importation rates, the spacing between rounds and the addition of primaquine to MDA with long lasting ACTs have little effect within the scenarios examined here. The proportion of the population reached by at least one MDA round per year has a very large influence on MDA effectiveness and should be the focus of operational efforts.

This exercise did not entail formal analysis of which differences between the models account for the variation in predicted impact of MDA. MDA can have an intense impact on transmission, at least in the short-term, making the transmission dynamics more complex than those analysed in the recent in-depth comparisons of models of RTS,S effects (13). Differences between the models in basic epidemiological quantities including duration of untreated infections and clinical immunity, may be relevant but have not generally been critically evaluated. For instance OpenMalaria simulates higher levels of acute illness in naïve hosts than does the Imperial model, and this means that if (as in these simulations), there is good access to care, low prevalence in OpenMalaria corresponds to higher force of infection, but less stable transmission than at lower coverage of case management.

A further source of variation between the models regarding impacts is the differences in assumptions about within-population heterogeneity in prevalence, which were not standardised in this exercise. In some of the models, as in reality, an average prevalence of 1% can only be maintained by simulating variability in susceptibility and/or response to infection between different hosts. Some of this is variation in space, but the models also address non-spatial variation in susceptibility between hosts in different ways. The extent of these sources of variability is critical for the stability of transmission. Temporal (seasonal) variation makes transmission less stable, at a given level of prevalence, while spatial



heterogeneity can make it more stable. Population sub-division may also be critically important. If there are many areas with zero prevalence and a few smaller areas with higher prevalence, simulations of small populations with 5-10% prevalence, diluted by unexposed individuals may be appropriate representations of 1% average prevalence. The size of such sub-populations (and their degree of interconnection, corresponding to the frequency of importations) can then be crucial, since stochastic extinction is much more likely in smaller populations.

Each model fixed the initial prevalence values for their simulations, but this could correspond to very different settings in terms of the immune status of the human population, the pattern of vectorial capacity, and correspondingly whether this represents long-term stable transmission, recent infection of a receptive human population, or the result of a temporary fluctuation in receptivity. Where an initial stable endemic state was used, this approximates only a subset of the settings where MDA might be considered. It does not consider epidemics: either where non-immune populations (such as displaced people) move into areas of high vectorial capacity, or where vectorial capacity temporarily increases (*e.g.* owing to unusual weather patterns). Some initial conditions lead to extinction of the parasite population even without MDA. It is then questionable whether there can be an incremental benefit of MDA. This may correspond to the reality in some epidemic situations, but there is an unanswered challenge in how to distinguish such settings in practice from others where MDA may make a critical difference.

The value of the present simulations is therefore mainly to show that there is a consensus on the relative influence of MDA operational characteristics. This states that reaching as many people as possible at least once should be the operational priority, whether this is achieved through high per-round coverage, multiple rounds that target different individuals, or optimising timing between rounds to treat different individuals. It should be noted that, under no circumstances do any of the models predict that MDA is an effective replacement for existing vector control and indeed the overarching message from this model comparison is that without some other change, such as improved vector control, the effects of MDA are likely to be transient.

The challenges in comparing the models would be even greater for formal comparisons of interruption of transmission than for reductions in prevalence, since uniform extinction criteria are not applicable given the difference in model structures. The quantitative predictions of impact are associated with substantial model uncertainty.

Future work may address these non-harmonised factors between the models and aim to give more comparable estimates of impact magnitude. Predictions of transmission interruption will also be developed by applying these models in standardised explicitly spatial contexts based on local epidemiological data and realistic operational constraints.

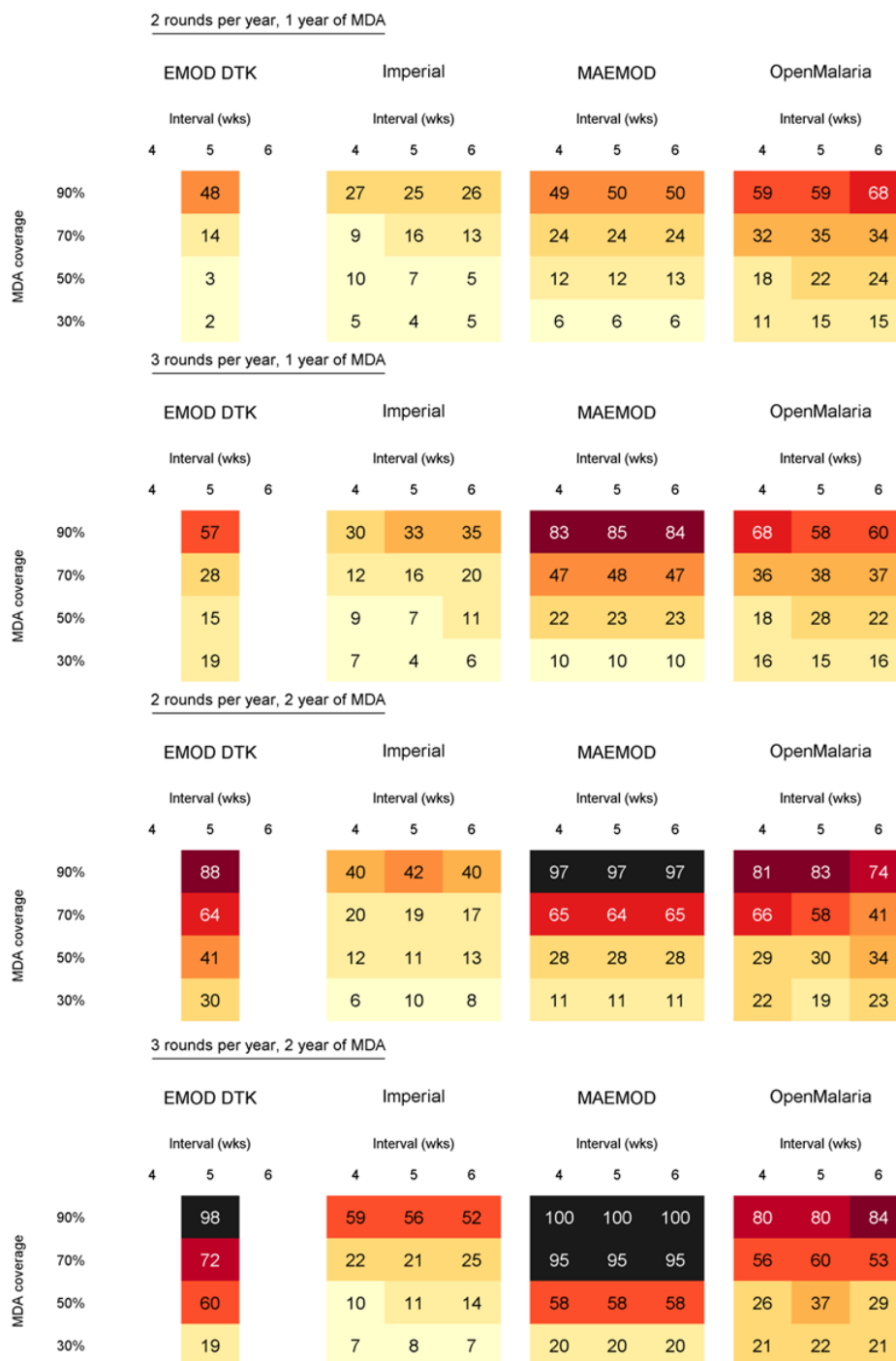
## Appendix: Summary of models of malaria transmission.

Model name	EMOD DTK	Imperial	MAEMOD	OpenMalaria
Institutional home	Institute for Disease Modelling (IDM)	Imperial College London (IC)	MORU	Swiss Tropical and Public Health Institute (Swiss TPH)
Type of model & references	Individual-based stochastic microsimulation (14, 15)	Individual-based stochastic microsimulations of malaria in humans linked to a stochastic compartmental model for mosquitoes (16)	Deterministic compartmental model described by differential equations (8) including drug action on each stage of the infection	Single location individual-based simulation of malaria in humans (17) linked to deterministic model of malaria in mosquitoes (18)
How infections are tracked	Tracks parasite densities of different surface-antigen types	Tracks membership of categories of infection (symptomatic, asymptomatic, submicroscopic, treated)	Tracks membership of categories of infection	Tracks parasite densities corresponding to different infection events
Relationship between EIR and prevalence	Immunity is acquired through cumulative exposure to different antigenic determinants (19) with heterogeneity in individual biting rates included	Immunity is acquired through cumulative exposure mosquito bites with heterogeneity in individual biting rates included	Subdivides population into non-immune & immune classes	Sub-models of infection of humans (20), and of blood-stage parasite densities with main immune effects controlling parasite densities (21)
Duration of infections	Infection duration based on malariatherapy (19) and cross-sectional survey data (22)	Infection duration based on fitting to asexual parasite prevalence data by age, transmission intensity & seasonality	Infection duration based on malariatherapy data and data from endemic areas	Infection duration based on malariatherapy data (21)
Impact of MDA or case management	Reduces blood-stage parasite densities according to age- and dose-specific PkPd (5) with the corresponding clearance and prophylactic effects. Prophylactic period based on PkPd studies (5)	Truncates infections and has subsequent prophylactic effect based on fitting pharmacokinetic/dynamic models to field studies	Post-treatment prophylactic period derived from field studies of time to next infection	Truncates infections, and has subsequent prophylactic effect based on pharmacokinetic/dynamic studies
Validation against MDA or MSAT trials	Evaluated against MACEPA MSAT	Evaluated against a controlled MDA	Fitted to an MDA trial in Cambodia	Fitted to the data of the Garki



	trial in Southern Zambia (unpublished)	trial (23) in Burkina Faso (model slightly optimistic about impact vs data), and the MACEPA MSAT trial in Southern Zambia (model matched data)	(24)	project (Matsari) (20), and evaluated against the MACEPA MSAT trial in Southern Zambia (7)
Infectiousness to mosquitoes	A function of mature gametocyte density and cytokine densities (19, 22)	Related to asexual parasite dynamics and lagged to allow for development of gametocytes	Infected individuals have a constant infectiousness	Lagged function of asexual parasite density (25)
Heterogeneity in exposure	Age-dependent biting (26) and configurable distribution of household-variability (the latter disabled in this analysis)	Included	Not included	Included
Initial state	-	Back-calculating required mosquito density to achieve given initial prevalence at an approximate steady state in the presence of treatment and LLIN	Set transmission rate to achieve given initial prevalence at an approximate steady state in the presence of treatment	Back-calculating required mosquito density to achieve given initial prevalence at an approximate steady state in the presence of treatment
Source of seasonality pattern	Rainfall and imputed temperature (27) driving larval habitat model fitted to clinical incidence patterns in Sinazongwe and Gwembe Districts	Rainfall data from Zambia combined with larval & adult mosquito model	Same EIR input as Imperial model	Based on pattern for southern Zambia used by (7)
Age structured model	Yes	Yes	No	Yes
Simulation of correlated rounds of intervention	Yes	Yes	No	Yes

The table summarises the characteristics and functionality of the models as applied in this exercise. The ACT modelled for this exercise was DHA-piperaquine. It was assumed that no antimalarial drug resistance was present throughout the modelled period. All the models are extensible to include other functionality (e.g. different drugs, effects of drug resistance, impact on drug resistance, vector bionomics and details of vector control, different initial conditions, other concomitant interventions). A detailed comparison of EMOD DTK, Imperial and OpenMalaria, including references to the data to which they are fitted, is available in a forthcoming paper on RTS,S (13).



**Figure A1 Percentage reduction in mean annual all-age PCR prevalence (PfPR<sub>2-10</sub>) in 3rd year after the intervention has ended**

Darker colours indicate larger reductions. This figures summarises the same results as Figure 2 in the main text, but with results shown for the interval (in weeks) between MDA rounds.

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