Malaria Policy Advisory Committee Meeting
10–12 April 2019, Geneva, Switzerland
Background document for Session 7

World Health Organization

Meeting report of the WHO Evidence Review Group on mass drug administration for malaria

11–13 September 2018, Geneva, Switzerland

Summary

Mass drug administration (MDA), the strategy of administering antimalarials to all age groups of a defined population (except those for whom the drugs are contraindicated) at the same time regardless of infection status, has recently received renewed interest for its potential to accelerate malaria elimination through rapid and sustained reduction of transmission.

In 2015, the World Health Organization (WHO) recommended that the use of time-limited MDA in combination with other malaria control measures could be considered in the following scenarios: in areas approaching interruption of *Plasmodium falciparum* transmission; in the Greater Mekong subregion (GMS) as a component of accelerated malaria elimination efforts; and in epidemics and complex emergencies to reduce morbidity and mortality. Since WHO's recommendation, new studies have been conducted in areas of low to moderate transmission in Africa and in the GMS, generating additional data on the role of MDA in rapidly reducing transmission. In light of the new data, WHO convened an evidence review meeting to revise and refine the current recommendations on MDA to accelerate malaria elimination, focusing on the evidence emerging from several studies in African countries and the GMS. Modelling studies and results of the update to the Cochrane Systematic Review were also presented and discussed at the meeting.

This meeting report provides a summary of the evidence presented, draft conclusions and a proposed update to the WHO recommendations. The report is submitted to the WHO Malaria Policy Advisory Committee (MPAC) for consideration.

Conclusions

Across all transmission settings:

- MDA may rapidly reduce, but does not interrupt, malaria transmission in the short term (1–3 months after the last round) across all transmission intensities when implemented along with vector control and case management.
- Short-term reductions in malaria transmission from MDA have only been sustained (4–36 months after the last round) in areas of very low to low transmission (RDT/microscopy parasite prevalence <10%) and in island settings with moderate transmission (up to 15% prevalence). Maintaining reductions in transmission after the last round of MDA requires additional

WHO/CDS/GMP/MPAC/2019.04

interventions, including vector control, case management, and intensified surveillance and response.

- Two factors strongly associated with the success of MDA in reducing malaria transmission in the short term are high coverage of the population with MDA (a large proportion of the population receiving at least one round of MDA), which may be achieved with more than one consecutive round per year, and focusing a second round on those missed in the first round.
- The decision to initiate an MDA campaign to accelerate elimination should be based on the balance between the risks of treating the whole eligible population, very few of whom (in a low transmission setting) may be at risk of malaria, and the potential benefits from cases averted. The decision to use MDA to rapidly reduce transmission should also consider whether MDA is cost-effective compared to other interventions.

In moderate to high transmission settings (parasite prevalence ≥10%):

- There is evidence from both a systematic review and the most recent research studies that MDA reduces the transmission of *P. falciparum* in moderate transmission settings (parasite prevalence 10–35%) in the first three months after the last round of MDA is completed, but the evidence is inconclusive from areas of high transmission (parasite prevalence ≥35%). Evidence suggests that the short-term impact of MDA programmes in moderate transmission settings has likely been enhanced by the presence of additional interventions, including vector control and case management.
- The evidence reviewed suggested that the reduction in malaria transmission from MDA could be sustained for up to three years in island settings in areas of moderate *P. falciparum* transmission up to a parasite prevalence of 15% when additional interventions are in place, including vector control, case management and intensified surveillance.

In very low to low transmission settings (parasite prevalence <10%):

- There is evidence from recent research studies that MDA reduces transmission of *P. falciparum* in the first three months after completion of the last round of MDA in low transmission settings (parasite prevalence 1–10%). However, there is no evidence that MDA, even in conjunction with vector control and good case management, can interrupt transmission. No evidence was available for review from very low transmission settings (parasite prevalence <1%).
- The impact of MDA on *P. falciparum* was sustained in many low transmission settings for more than 30 months when additional interventions were deployed, including vector control, community-based case management and intensified surveillance.

Impact on *P. vivax:*

- Two studies of MDA in the GMS using an artemisinin-based combination therapy (ACT) plus a single low dose of primaquine (PQ) reported differing results for *P. vivax*, with one study demonstrating only a short-term reduction in *P. vivax* transmission and the other study finding no effect.

- Historical and recent evidence shows a significant short-term reduction in *P. vivax* transmission, with lower incidence maintained until the following transmission season and up to six months in temperate areas, following the deployment of PQ mass prophylactic treatment for 14 days in combination with other malaria control interventions.

Impact on antimalarial resistance:

- Early results from modelling studies indicate that the risk of MDA in selecting for resistant strains rises with an increasing rate of importation of resistant strains into the MDA area. Conversely, the risk may decrease with increased access to antimalarial medicines that were not used for the MDA regimen in the immediate post-MDA period.

Proposed update to current recommendations on MDA

Based on the above conclusions, the ERG proposes that the existing recommendations on MDA be updated and replaced by the following draft recommendations, which are submitted for consideration to the WHO MPAC.

1. Use of MDA to accelerate progress towards elimination (i.e., significant reductions in malaria transmission sustained over time) of *P. falciparum* malaria can be considered in areas of very low to low transmission (parasite prevalence <10%) where there is good access to effective treatment and effective implementation of vector control and surveillance, and limited risk of re-introduction of infection. Additionally, MDA can be considered in small islands (<500 000 population) with moderate transmission (*P. falciparum* parasite prevalence 10–15%) where there is limited risk of re-introduction of parasites, effective treatment, and effective implementation of vector control and surveillance.

2. In settings with moderate to high transmission, MDA may produce a short-term reduction in malaria burden, but so far there is no evidence that MDA, with or without additional interventions, will accelerate progress towards elimination. More evidence should be gathered to determine whether repeated rounds of MDA over multiple years in conjunction with other interventions in these settings could sustain reduced transmission and accelerate progress towards elimination.

3. Mass primaquine prophylactic treatment, requiring pre-seasonal MDA with daily administration of primaquine for two weeks, can be considered as a component of *P. vivax* elimination strategies in temperate regions, taking into consideration G6PD deficiency.

4. Given the threat of *P. falciparum* multidrug resistance and the WHO call for malaria elimination in the Greater Mekong subregion (GMS), MDA should be considered as a component of accelerated malaria elimination efforts in the GMS where there is good access to effective treatment and effective implementation of vector control and surveillance, and limited risk of re-introduction of infection. However, because of prevalent multidrug resistance in the region, the options are limited for effective antimalarials that can be used in MDA.

5. Use of time-limited MDA to rapidly reduce malaria morbidity and mortality may be considered for epidemic control as part of the initial response, along with the urgent introduction of other interventions.[1]

6. Use of time-limited MDA to reduce malaria morbidity and mortality may be considered in complex emergencies, during exceptional circumstances when the health system is overwhelmed and unable to serve the affected communities.[1]

7. Medicines used for MDA must be of proven efficacy in the implementation area and preferably have a long half-life. WHO recommends that a medicine different from that used for first-line treatment be used for MDA to reduce the risk of development of resistance. Programmes should include drug safety monitoring during MDA campaigns. Drug efficacy should be monitored after the campaign to identify potential emergence of resistance to the antimalarial medicines deployed for MDA.

8. WHO supports the need for more research on the optimum methods for implementing MDA programmes, promoting community engagement and compliance with treatment, and evaluating the effectiveness of MDA programmes. Modelling can help guide the optimum method for administering MDA in different epidemiological circumstances and help predict its likely impact.

Abbreviations

ACT	artemisinin-based combination therapy
AP	artemisinin-piperaquine
DP	dihydroartemisinin-piperaquine
ERG	Evidence Review Group
G6PD	glucose-6-phosphate dehydrogenase
GMP	Global Malaria Programme
GMS	Greater Mekong subregion
IRS	indoor residual spraying
LLIN	long-lasting insecticidal net
MDA	mass drug administration
MPAC	Malaria Policy Advisory Committee
MPPT	mass primaquine preventive treatment
NMCP	national malaria control programme
P.	*Plasmodium*
PCR	polymerase chain reaction
PQ	primaquine
RDT	rapid diagnostic test
WHO	World Health Organization

[1] No evidence was reviewed related to this recommendation and so it has not been updated.

1. Background

Mass drug administration (MDA) for malaria is defined by the World Health Organization (WHO) as the *administration of antimalarial treatment to all age groups of a defined population or every person living in a defined geographical area (except those for whom the medicine is contraindicated) at approximately the same time and often at repeated intervals (1,2).* It is one of the recommended interventions for preventive chemotherapy. Similar to chemoprophylaxis, intermittent preventive treatment of infants and pregnant women, and seasonal malaria chemoprevention, MDA deploys antimalarial medicines to prevent malaria infections and their consequences. MDA may be deployed for two distinct but complementary objectives: 1) to rapidly reduce transmission of malaria, which may accelerate progress towards elimination and control malaria epidemics, and 2) to rapidly reduce morbidity and mortality during epidemics and complex emergencies *(3)*.

Although MDA has been historically a key component of malaria control and elimination strategies, WHO has not promoted this intervention for some time; however, the role of MDA has recently received renewed interest for its potential to accelerate progress towards elimination through the rapid reduction of parasites in the human reservoir, which may then lead to a reduction in malaria transmission. After reviewing the evidence on the use of MDA in specific epidemiological settings in 2015 *(4)*, WHO recommended the use of MDA to interrupt *Plasmodium falciparum* transmission in areas approaching elimination; to reduce the risk of multidrug resistance spread in the Greater Mekong subregion (GMS) by contributing to *P. falciparum* elimination; during malaria epidemics as part of the initial response; and in exceptional complex emergencies to reduce morbidity and mortality *(5,6)*.

In the years following the publication of these recommendations, several large-scale trials and MDA campaigns were implemented across the transmission continuum, permitting the assessment of the potential role of MDA in interrupting or accelerating reductions in transmission in combination with other core interventions. In addition, a Cochrane Systematic Review on MDA for malaria, published in 2013 *(7)*, has been updated and additional modelling studies completed. As a result of the availability of new research and programmatic evidence, WHO convened an Evidence Review Group (ERG) to revise and refine the current recommendations, focusing on the role of MDA in decreasing transmission and accelerating progress towards elimination.

2. Objectives

The specific objectives of the ERG were to:

1. determine the effectiveness of MDA combined with other core interventions in reducing malaria incidence and prevalence of *P. falciparum* and *P. vivax* malaria in areas of low, moderate and high transmission, with particular attention to the effects of vector control, case management and intensified surveillance on the effectiveness of MDA, and the determinants of sustained post-MDA reduction in malaria transmission; and
2. review new evidence on the impact of MDA in areas of low to very low transmission in relation to current WHO recommendations on MDA for interrupting the transmission of *P. falciparum* malaria in areas approaching elimination and reducing the spread of multidrug resistance in the GMS.

3. Process

The WHO Secretariat of three units of the Global Malaria Programme (GMP) – 1) Prevention, Diagnostics and Treatment; 2) Elimination; and 3) Drug Efficacy and Response – jointly planned the meeting. Nine independent experts in malaria epidemiology, elimination and chemotherapy, and methodology specialists in the assessment of data from applied field research were convened, together with 18 participants representing national malaria control programmes (NMCPs) and collaborating technical research institutions, who were invited to present recent results from MDA field studies, MDA campaigns, systematic reviews and modelling studies. The pre-reads prepared by the presenters, together with relevant WHO reports, were shared with all the participants prior to the meeting (Annex 1). Six observers representing academia, philanthropic foundations and funding agencies, together with seven members of the WHO Secretariat, completed the list of participants (Annex 2).

The trials, reviews, programmatic data and studies were presented in plenary sessions during the first two days of the meeting. The sessions listed below were each followed by plenary discussions:

- Cochrane Systematic Review update of MDA for malaria
- MDA as accelerator of *P. falciparum* elimination in the African Region
- Modelling the contribution of MDA to malaria elimination and drug resistance
- MDA as accelerator of *P. falciparum* elimination in the GMS
- Other studies on impact of MDA on malaria transmission in the African Region
- Mass primaquine preventive treatment (MPPT) as an accelerator of *P. vivax* elimination.

The last day of the meeting was restricted to the independent experts and WHO Secretariat, focusing on the discussion of the meeting conclusions and development of the draft recommendations to be submitted to MPAC in March 2019. GMP provided a set of questions to the independent experts to facilitate the development of the draft recommendations. The questions and answers drafted by the ERG are attached in Annex 3.

The meeting report was compiled based on the meeting pre-reads, presentations and discussions that took place during the ERG meeting. The details of the field studies presented are summarized in Annex 4. All participants were invited to review the draft and provide further input to the final report.

4. Evidence review

Categories of transmission intensity

Based on the transmission levels presented in the WHO framework for malaria elimination, measured by microscopy or conventional rapid diagnostic tests (RDTs) *(8)*, the studies reviewed at the meeting are presented by country and transmission intensity, as shown in Table 1.

Table 1. Studies presented by category of transmission intensity

Level of transmission	Parasite prevalence	Country
High	≥35%	Uganda, Zambia
Moderate	10–35%	Comoros Islands (Anjouan and Grande Comore)
Low	1–10%	Mozambique, Zambia, Gambia, Myanmar, Viet Nam, Cambodia, Lao People's Democratic Republic
Very low	0–1%	None available

Cochrane Systematic Review update on MDA for malaria

A Cochrane Systematic Review published in 2013 reported on the impact of MDA on malaria based on 32 published studies *(7)*.

The review was updated in 2018 with revised inclusion criteria to select more rigorous study designs with control groups and balanced co-interventions across study arms. A draft of the updated review was presented at the meeting. The effect of MDA was assessed on the interruption of transmission in very low to low transmission settings (<10% prevalence) and on the reduction of malaria transmission in moderate to high transmission areas (≥10% prevalence). As a secondary objective, MDA-associated adverse events were evaluated. The primary outcomes were parasite prevalence, parasite incidence (i.e., incidence of infection from active surveillance), and confirmed malaria illness incidence (i.e., confirmed clinical infection from passive surveillance). Outcomes were stratified by pre-MDA (prior to the first round of MDA), during MDA (time period between the first and last rounds of MDA), and post-MDA (following the last round of MDA, categorized as <1, 1–3, 4–6, 7–12, 13–18, 19–24, 25–30, and 31–36 months) (*Shah, unpublished report*).

Out of 358 records identified from the search, 36 full-text articles were assessed for eligibility and nine studies met the inclusion criteria: five cluster-randomized trials were included in a quantitative synthesis (one additional trial was not analysed due to insufficient data) and three non-randomized (controlled before-and-after) studies were analysed separately. Two out of the 10 studies reviewed at the ERG meeting were also included in the Cochrane analysis.

Two cluster-randomized trials took place in Zambia and The Gambia in areas of moderate to high transmission. In Zambia, four rounds of MDA with dihydroartemisinin-piperaquine (DP) were conducted between 2015 and 2016, in combination with indoor residual spraying (IRS), long-lasting insecticidal nets (LLINs) and enhanced community case management. In The Gambia, one round of MDA with sulfadoxine-pyrimethamine plus artesunate was conducted in 1999 *(9,10)*. Based on the analysis of these data (*Shah, unpublished report*):

- MDA probably leads to little or no reduction in parasite prevalence at 1–3 months (n=1 study) and 4–6 months (n=1 study) post-MDA (*moderate certainty evidence*), and MDA may lead to little or no difference at 13–18 months (n=1 study) post-MDA compared to no MDA (*low certainty evidence*).
- MDA probably reduces parasite incidence at 1–3 months (n=1 study) post-MDA compared to no MDA (*moderate certainty evidence*), but, based on the available evidence, the effect at 4–6 months (n=1 study) post-MDA is unknown (*very low certainty evidence*).

- MDA may lead to no reduction in confirmed malaria illness incidence at 1–3 months (n=1 study) post-MDA compared to no MDA (*low certainty evidence*).

Three cluster-randomized trials were carried out in Myanmar, Zambia and Zanzibar, categorized as very low to low transmission settings (<10% prevalence) *(9,11,12)*. In Myanmar, three rounds of MDA with DP plus primaquine (PQ) were administered in combination with LLINs. In Zambia, four rounds of MDA with DP were administered with IRS, LLINs and enhanced community case management. In Zanzibar, two rounds of DP plus PQ were administered with IRS and LLINs. Based on analysis of these data (*Shah, unpublished report*):

- It is unknown whether MDA has an effect on the reduction of *P. falciparum* parasite prevalence at all post-MDA time points from <1 month through 31–36 months (*very low certainty evidence*).
- MDA probably reduces parasite incidence at 1–3 months post-MDA compared to no MDA (*moderate certainty evidence*).
- It is unknown whether MDA has an effect on the reduction of confirmed malaria illness incidence in the period between 1–3 months and 13–18 months post-MDA (*very low certainty evidence*).

P. vivax parasite prevalence was also reported in the study in Myanmar *(11)*. Based on evidence from this study, MDA may reduce *P. vivax* parasite prevalence at <1 month (*low certainty evidence*), but MDA may have little or no effect at 1–3 months post-MDA (*low certainty evidence*); it is unknown whether MDA has an effect at post-MDA time points from 4–6 months through 31–36 months (*very low certainty evidence*) (*Shah, unpublished report*).

Three non-randomized studies conducted before 1980 in moderate to high transmission areas in Burkina Faso, Kenya and Nigeria were also included in the Cochrane Systematic Review update *(13–15)*. In Burkina Faso, either seven ("low frequency") or 15 ("high frequency") MDA rounds of amodiaquine-primaquine or chloroquine-primaquine were administered in 1960–1961 with no co-interventions. In Kenya, two rounds of MDA with pyrimethamine were administered in 1953–1954 with no co-interventions. In Nigeria, either nine ("low frequency") or 23 ("high frequency") rounds of MDA with sulfadoxine-pyrimethamine were administered between 1970 and 1975. All studies reported the outcome of *P. falciparum* parasite prevalence. During the MDA rounds, parasite prevalence decreased in all studies (*Shah, unpublished report*). Two studies provided data at 1–3 months post-MDA (Burkina Faso and Kenya). Reductions were seen in the Kenyan study and in the low frequency arm but not the high frequency arm of the Burkina Faso study. Only one study (Kenya) reported outcomes at 4–6 and 7–12 months post-MDA and found sustained, but smaller, reductions in parasite prevalence over time (*Shah, unpublished report*).

Given the limited number of studies evaluated after the stratification by endemicity and time period in the Cochrane Systematic Review update, it was not possible to determine whether factors such as the drug's prophylactic duration, MDA coverage, concomitant interventions, or risk of re-introduction may modify the effect of MDA (*Shah, unpublished report*).

Key conclusions from the Cochrane Systematic Review update on MDA for malaria:

- In moderate to high transmission settings, there was evidence of short-term reduction (1–3 months post-MDA) in *P. falciparum* incidence, but no evidence of an effect on parasite prevalence or confirmed malaria illness incidence at any post-MDA time points.
- In very low to low transmission settings, there was evidence of a short-term reduction (1–3 months post-MDA) in *P. falciparum* incidence, but there was insufficient evidence to

determine whether there were any effects on parasite prevalence or confirmed malaria illness incidence at longer term post-MDA time points.

- Evidence from a single study suggests that MDA may reduce *P. vivax* parasite prevalence at <1 month, but MDA may have little or no effect at 1–3 months. There is insufficient evidence to determine the effect at other post-MDA time points.

New evidence on impact of MDA by level of malaria transmission and location

Evidence from nine studies (one ongoing and eight completed) deploying MDA in Africa and the GMS was presented to the ERG members.[2]

These studies have been stratified by transmission intensity in order to facilitate comparison of the results. The list of the studies reviewed is presented in Annex 4.

Moderate to high transmission settings (>10% prevalence)

The following studies located in settings with moderate to high transmission were presented:

Table 2. Studies located in moderate to high transmission settings

Level of transmission	Parasite prevalence (RDT)[3]	Country	Study design	Target population[4]	Drug, number of rounds	Vector control interventions
High	51% (<6 years old)	Zambia[5]	Randomized	45 442	DP, four rounds	LLINs, IRS
	35% (all ages)	Uganda	Non-randomized	16 777	DP, four rounds	LLINs, IRS
Moderate	13.5% (6 months to 16 years old)	Comoros Islands, Anjouan	Non-randomized, interrupted time series	321 635	AP+PQ or AP only, three rounds	LLINs
	10.6% (<5 years old)	Comoros Islands, Grande Comore	Non-randomized, interrupted time series	433 348	AP + PQ, two rounds	LLINs

Note: DP: dihydroartemisinin + piperaquine; AP: artemisinin + piperaquine; LLINs: long-lasting insecticidal nets; IRS: indoor residual spraying

High transmission (≥35% parasite prevalence)

Data were available for review from two studies:

- a community randomized controlled trial in Zambia during 2015 and 2016 to assess the impact of four rounds of MDA with a follow-up period of 18 months (until May 2016) *(9)*; and
- a two-year (2017–-2018) quasi-experimental study in Uganda of the impact of four rounds of IRS in combination with MDA (*Echodu, unpublished report*).

[2]An additional study in Cambodia evaluating three rounds of prophylaxis with DP was reviewed but determined not to meet the definition of an MDA because antimalarials were given only to volunteers and their families and not to the entire population of a geographic area.
[3] Parasite prevalence (RDT) at baseline
[4] Population targeted for treatment
[5] Results from this study were also included in the Cochrane Review.

Both studies combined MDA with LLINs and IRS. In Zambia, the standard of care package also included improved surveillance, community engagement and expansion of community case management with an increase in the number of community health workers (*Eisele, unpublished report*). In Uganda, case management with ACTs was widely accessible from all health clinics in the study area (*Echodu, unpublished report*).

In Zambia, four rounds of MDA had no immediate impact on parasite prevalence in children or on confirmed malaria incidence compared to the standard of care, although there was an immediate, short-term reduction in the cumulative incidence of *P. falciparum* infection measured by polymerase chain reaction (PCR) in the MDA group (*Eisele, unpublished report*). As the cohort ended three months following the last MDA round, it is unknown whether there was a sustained decrease in the infection incidence in Zambia. In Uganda, there was a large decrease in parasite prevalence in the two intervention arms (LLINs + IRS and LLINs + IRS + MDA) compared to the control arm (LLINs only); however, there was no statistically significant difference in the reduction between the LLINs + IRS + MDA arm and the LLINs + IRS arm (*Echodu, unpublished report*), suggesting that MDA had no effect. This study was limited, however, by having only one site per arm.

The strategy currently adopted by the National Malaria Elimination Programme of Zambia was also presented. Community-wide MDA is now implemented in eligible health facility catchment areas of the country, defined as those with a high coverage of LLINs and/or IRS, enhanced community case management, and a functional surveillance system capable of responding to index cases post-MDA, with between 50 and 500 cases per 1000 population. Following these criteria, two rounds of programmatic MDA were conducted in 2017, and two additional rounds were planned for 2018. Preliminary findings suggest a benefit of combining a full package of malaria interventions including MDA, but the analysis is still ongoing (*Busiku, unpublished report*).

Moderate transmission (10–35% parasite prevalence)

Data were available for review from two studies:

- an interrupted time series analysis of programmatic implementation of three rounds of MDA on Anjouan island in Comoros deployed in 2012 with a follow-up period of 18 months *(16)*; and
- an interrupted time series analysis of programmatic implementation of two rounds of MDA on Grande Comore (Ngazidja Island) in Comoros deployed in 2013 (*Bacar, unpublished report).*

MDA in combination with vector control has been used in three islands of the Comoros archipelago with a highly significant reduction in malaria transmission (*(16)* and *Bacar, unpublished report)*. Reports from two of the islands were available for review. In Anjouan Island, three rounds of MDA (approximately half of the population receiving AP and the other half receiving a single low dose of PQ in addition to the ACT) rapidly reduced malaria transmission, achieving approximately a 99% reduction in malaria incidence one year after the last round of MDA. Despite these gains, no additional difference in impact was seen in the areas receiving PQ. In Grande Comore, two monthly rounds of MDA with an ACT plus a single low dose of PQ were deployed to accelerate reductions in malaria transmission. In both cases, a rapid decline in *P. falciparum* malaria incidence was observed in the period immediately post-MDA. The effect was sustained in Anjouan for at least five years and in Grande Comore for three years. In both islands, there was intensified surveillance following the MDA campaigns, including proactive and reactive case detection.

Key factors in the success of the MDA campaign were community mobilization and participation to improve MDA uptake coverage, and the involvement of a large number of trained drug dispensers and

supervisors. In Anjouan Island, mobilization and training of the local team was done for three months to ensure correct deployment of the intervention, and a campaign to inform and engage the population was undertaken as well. On this island, the average coverage rates achieved varied from 85.7% to 92.9% *(16)*.

In Anjouan Island, the monitoring and treatment of travellers was also done in an attempt to control and monitor importation of parasites. At the airport and wharfs of the island, travellers were asked to complete information surveys and given antimalarial drugs for self-administration. Individual travellers were asked to visit a malaria diagnostic laboratory where they could have free microscopic testing for malaria infection *(16)*.

Very low to low transmission settings (<10% prevalence)

Based on the available evidence, the impact of MDA was evaluated for low transmission areas in Africa and the GMS. The following six studies were available for review:

Table 3. Studies located in low transmission settings

Level of transmission	Parasite prevalence (RDT)[6]	Country	Study design	Target population[7]	Drug, rounds	Vector control interventions
Low	7.5% (all ages)	Gambia	Non-randomized	4312 (year 2014) 4189 (year 2015)	DP, two rounds	LLINs, IRS
	9% (all ages)	Mozambique	Non-randomized	52 581 (year 2015) 61 868 (year 2016)	DP, four rounds	LLINs, IRS
	8% (<6 years old)	Zambia[8]	Randomized	37 694	DP, four rounds	LLINs, IRS
	6% (all ages)	Myanmar Viet Nam Cambodia Lao People's Democratic Republic	Randomized	4423	DP + PQ, three rounds	LLINs
	5.5% (all ages)	Myanmar (Eastern Kayin State)	Non-randomized	12 465	DP + PQ, three rounds	LLINs
	2.7% (≥18 years old)	Myanmar (Southern Kayin State)	Randomized	4618	DP + PQ, three rounds	LLINs

- a two-year pre-post, non-controlled study in The Gambia of the impact of a single MDA round per year for two years (2014 and 2015) *(17)*;
- a pre-post *quasi-experimental* study of a community mobilization campaign followed by one round of IRS and two rounds of MDA per year for two consecutive years (from November 2015

[6] Parasite prevalence (RDT) at baseline.
[7] Population targeted for treatment.
[8] These studies were also included in the Cochrane Review.

to February 2017) in Mozambique, followed by reactive focal drug administration on top of standard case management and bed-net distributions (*Galatas, unpublished report*);

- a community-randomized controlled trial in Zambia to assess the impact of two rounds of MDA two to five months apart during 2015 and 2016 *(9)*;
- a multisite, stratified, cluster-randomized trial in Myanmar, Viet Nam, Cambodia and Lao People's Democratic Republic between 2013 and 2017 to assess the effectiveness, safety, tolerability and acceptability of three rounds of MDA, with a follow-up period of 24 months in Myanmar and Viet Nam and 12 months in Cambodia and Lao People's Democratic Republic (*von Seidlein, unpublished report*);
- a targeted MDA study in transmission hotspots in four townships of Eastern Myanmar undertaken from 2014 to 2017, with follow-up still ongoing *(18–20)*; and
- a community-randomized controlled study of three rounds of MDA one month apart in 2015 in 'hotspot' villages near the Thai border in Southern Kayin State, Myanmar, with a follow-up period of 33 months (*McLean, unpublished report*).

In all these studies, MDA in combination with other interventions significantly reduced the malaria burden over the short term, but interruption of transmission was not achieved. In the study area in The Gambia, lower malaria prevalence was observed in the first three months post-MDA *(17)*. Similarly, in Mozambique (*Galatas, unpublished report*) and in Zambia (*Eisele, unpublished report)*, high vector control in combination with four rounds of MDA significantly reduced the malaria burden. In the GMS, a cluster-randomized trial in Myanmar, Cambodia, Viet Nam and Lao People's Democratic Republic that targeted a total of 16 villages observed that the *P. falciparum* prevalence had fallen considerably in the MDA villages three months after the last round of MDA (*von Seidlein, unpublished report*). In Eastern Myanmar, 50 hotspots received MDA in five campaigns, and the *P. falciparum* infection prevalence 12 months after MDA decreased by a median of 92% compared to pre-MDA levels *(18)*. The study conducted in Southern Myanmar, which also targeted hotspots of high transmission, observed a significantly lower *P. falciparum* infection prevalence in the intervention villages one month after the last round of MDA (*McLean, unpublished report).* Consistent with what has been described in other settings, a decrease in the malaria burden in the control arm was also observed during the study period, although to a much lesser degree than observed in the intervention arm (*McLean, unpublished report)*.

The long-term impact of MDA in reducing *P. falciparum* prevalence and incidence varied across sites. In The Gambia, the reduction in prevalence was sustained over two years in the areas of low transmission, but not in the areas of moderate transmission; a reduction in the risk of clinical malaria was seen throughout the transmission season *(17)*. During the second year of MDA rounds in Mozambique, the prevalence of malaria did not decline further (*Galatas, unpublished report*). In the GMS multisite trial, the *P. falciparum* prevalence one year after the last round of MDA was very low and even reached zero in four of the eight intervention villages, suggesting that in low transmission settings, MDA in combination with additional community-based strategies can help reduce, interrupt and sustain the reduction in *P. falciparum* transmission over a one-year period. The impact was seen to vary by country, being higher in villages with a baseline prevalence of *P. falciparum* over 5%. When comparing intervention and control arms, the prevalence of infection increased steadily over the nine months post-intervention, partly attributed to re-introduction from surrounding areas. However, this effect seems to have been mostly driven by sites located in a single county, given that it was not reflected at the village level for five out of eight of the intervention villages (*von Seidlein, unpublished report*). On the other hand, consistent with what has been seen in other settings, such as in Zambia or Myanmar (*Eisele, unpublished report; McLean, unpublished report*), a substantial reduction in malaria

transmission was also seen in the control villages that did not receive MDA. This reduction is attributable to the increased access to early diagnosis and treatment and the LLINs provided to all villages in the study (*von Seidlein, unpublished report*). In Southern Kayin State of Myanmar, the difference in *P. falciparum* prevalence between the intervention and control arms remained significant only up to three months after last round of MDA (as the prevalence in the control arm continued to decline over time with access to early diagnosis and treatment) (*McLean, unpublished report*), whereas in Eastern Kayin State, the reduction has been sustained for 20 months and follow-up is continuing *(18)*.

The available evidence shows that, in Mozambique, high vector control and reactive focal drug administration (*administering drugs to a subset of a population in a given area in response to detection of malaria cases at health facility levels (1)*) have been able to sustain the achieved low prevalence up to one year after the MDA (*Galatas, unpublished report*). In Zambia, malaria parasite prevalence in children remained low (87% reduction from baseline) up to 15 months after the last round of MDA with sustained high vector control coverage and improved access to diagnosis and treatment of malaria (*Eisele, unpublished report*), although there was no difference in malaria indicators between the intervention and control communities.

Community engagement campaigns were done in Mozambique prior to the first round of MDA, and reported LLIN usage increased significantly (*Galatas, unpublished report*). Further concomitant interventions implemented in the other studies that may have also contributed to the effectiveness of the package of interventions include intensified surveillance and community case management in Zambia and sensitization meetings in The Gambia prior to the trial. Intensive community engagement activities were also conducted in the GMS multisite trial prior to MDA in order to encourage uptake *(19, 20)*; of the people residing in the eight intervention villages during the three months of MDA, 86% completed at least one round and 57% completed the three rounds of MDA (*von Seidlein, unpublished report*). Along the same lines, community engagement activities that aimed to ensure understanding and acceptance of the strategy were also performed in the two studies located in Myanmar (*(18,23)* and *McLean, unpublished*). In Eastern Myanmar, community-based malaria posts provided increased access to early diagnosis and treatment to all villages, which was seen to help in decreasing the incidence of *P. falciparum* malaria in these hard-to-reach regions of the country *(18)*. Evidence of declines in malaria incidence with community-based malaria posts in the GMS has been reported elsewhere *(24,25)*.

Most low-density artemisinin- and piperaquine-resistant infections were cleared effectively with the available drugs. However, it was observed that higher density infections recrudesced more frequently, pointing to the need to closely monitor the efficacy of the ACTs deployed (*von Seidlein, unpublished report*). In Eastern Myanmar, the prevalence of wild-type genotype for K13 molecular markers of artemisinin resistance was monitored, and no evidence of worsening drug resistance was observed after drug deployment *(18)*.

In Southern Myanmar, *P. vivax* prevalence also decreased in the month following the last round of MDA, but the decrease was not sustained into the third month post-MDA (*McLean, unpublished*). By contrast, in Eastern Myanmar, little change in *P. vivax* incidence was observed during the study *(18)*.

Monthly intermittent preventive treatment to high-risk populations

A cluster-randomized trial conducted along the Cambodia–Thailand border in 2016 compared the effectiveness, safety and tolerability of monthly intermittent preventive treatment compared to focused screening and treatment of volunteers from military camps and their dependents (*Wojnarski,*

unpublished report). The intervention included monthly three-day course administration of DP plus low-dose weekly PQ for 12 weeks. Both groups had access to effective malaria diagnosis and treatment. Volunteers also received either insecticide-treated uniforms or water-treated uniforms based on cluster assignment. In the MDA arm, no benefit was observed from the insecticide-treated uniforms over drug therapy (*Wojnarski, unpublished report*). Significant reductions in *P. falciparum* incidence were seen up to six months post-intervention, while the impact on *P. vivax* incidence was modest, suggesting that reduction of *P. vivax* incidence in these settings will require different approaches (*Wojnarski, unpublished report*). This study was not included in the review, as the chemoprevention strategy deployed did not reach the entire population and, therefore, did not meet the definition of MDA.

Key conclusions about the impact of MDA in Africa and the GMS:

- In high transmission settings (parasite prevalence ≥35%), data were limited to two studies, neither of which showed a clear short-term effect of MDA on malaria burden.
- In moderate transmission settings (parasite prevalence 10–35%), MDA had a clear short-term effect in reducing malaria transmission when combined with vector control and case management, but the decline was not sustained in the long term.
- In island settings with moderate transmission up to 10–15% parasite prevalence, the short-term reductions in transmission resulting from MDA were sustained for up to three years when combined with vector control, case management, intensified surveillance and community engagement.
- In areas with low transmission (parasite prevalence 1–10%), MDA had a clear, short-term effect on malaria parasite prevalence and incidence when combined with vector control, case management and intensified surveillance. There was some evidence that these gains could be maintained over one or more years when combined with other interventions such as increased access to community-based diagnosis and treatment.
- No studies were reviewed from areas of very low transmission (parasite prevalence <1%).
- Despite the significant malaria reductions achieved with MDA in areas with low transmission intensity, no interruption of transmission (zero local cases) resulting from MDA has been documented.
- In areas with low transmission affected by multidrug resistance, the combination of increased access to early diagnosis, prompt treatment by community health workers and deployment of MDA has significantly decreased *P. falciparum* transmission, with many villages free from *falciparum* malaria for at least six months. Therefore, this package of interventions should be considered together with effective vector control in order to accelerate progress towards elimination in the region.
- No evidence of increased artemisinin or partner drug resistance has been documented related to MDA with ACTs, but further research and continuous monitoring of the effectiveness of ACTs are needed in areas considering MDA campaigns.
- MDA with ACTs has been shown to reduce transmission of *P. vivax* malaria in the short term, but there have been few studies addressing the impact of MDA on *P. vivax* in tropical areas.

Modelling the impact of MDA on malaria elimination and drug resistance

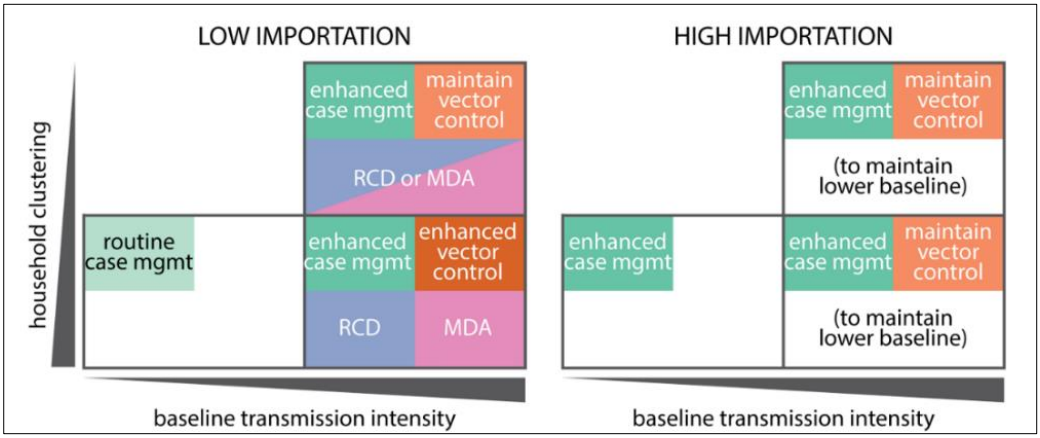
Testing combinations of strategies in the field is extremely challenging, particularly in terms of assessing the impact of multiple interventions in different epidemiological settings. In addition, the evaluation of the impact of different interventions in low transmission settings requires a large sample size, which is not always feasible. Given these limitations of field research, mathematical modelling can be a valuable approach to understanding the potential impact of different interventions across multiple epidemiological contexts.

Results from a consensus modelling effort indicate that the immediate reduction in transmission resulting from MDA in low transmission settings would be temporary and that, in the absence of high coverage with other interventions, such as vector control, transmission would return to pre-MDA levels. A key determinant of simulated effectiveness is the proportion of the population treated in a year, irrespective of whether people are treated through high coverage in a single round or new individuals are reached through implementation of several rounds. MDA is predicted to be more effective if continued over two years rather than one year, and if done at the time of year when transmission is lowest *(26)*.

Using household models of health facility catchment areas in the Lake Kariba region of the Southern Province of Zambia *(27)*, the role of a limited MDA programme for one to two years in combination with LLIN distribution, IRS, case management and reactive case detection was investigated. Additional hypothetical intervention scenarios were also tried, including counterfactuals. According to the model results, MDA can be an accelerator of malaria elimination if the following preconditions are met: excellent case management, effective vector control, low rates of parasite importation, good MDA coverage and appropriate timing of rounds (*Gerardin, unpublished report*). The same modelling exercise indicated that in low transmission areas with highly clustered households and low parasite importation rates, elimination can be achieved without the help of MDA if 100% of symptomatic cases are treated. However, MDA may play a substantial role in achieving elimination when case management is suboptimal, the MDA campaign is conducted early in an area's trajectory towards elimination, and thus a substantial infectious reservoir remains. In high transmission areas with dispersed households, elimination can be achieved when parasite importation rates are low or negligible, 100% of symptomatic cases are treated, and reactive case detection is very well implemented. In these situations, MDA has a small acceleration effect. In situations where case management and reactive case detection are not optimally implemented or where parasite importation rates are high, MDA can increase the likelihood of elimination being achieved, even though the overall probability of elimination remains low.

In conclusion, according to the model, the impact of MDA in accelerating the malaria elimination strategy depends on the baseline transmission intensity, household clustering, parasite importation rate, and quality and coverage of case management, reactive case detection and vector control (*Fig. 1*).

Fig. 1. Case scenarios and recommended elimination strategy



Source: Jaline Gerardin. Modelling intervention mixes in combination with MDA to accelerate malaria elimination. Institute for Disease Modelling. Unpublished report.

Also using data from Zambia, a conceptual, individual-based stochastic model of malaria transmission was developed to estimate the probability of resurgence after deployment of MDA and different co-interventions (*Smith, unpublished report*). The modelling showed that the two determinants of resurgence are the residual transmission (persistence of malaria transmission following the implementation in time and space of a widely effective malaria programme *(1)*) and the routine case management coverage for remaining cases. In this context, the concomitant interventions needed for both transmission reduction and significant clearance of low-density infections are vector control and case management deployed at high coverage levels (>80%). High-level coverage of early detection and treatment following MDA may be sufficient to avert resurgence by removing the introduction of gametocytes from imported cases (*Smith, personal communication*). The model also indicated that MDA may lead to elimination by stochastic extinction in areas with a relatively low reproduction number (R_0) when applied at very high coverage in combination with vector control interventions in relatively small populations *(28)*. This was shown by Kaneko et al. in Aneityun Island, Vanuatu *(29)*.

Models have also been used to explore the effects of MDA implementation on the spread of drug resistance. Results of an individual-based stochastic model evaluating the impact on drug resistance of high coverage of MDA with DP in populations of 40 000 and 300 000 individuals were presented at the meeting (*Nguyen, unpublished report*). The model simulations indicated that MDA creates a genetic bottleneck that makes gene frequencies associated with drug resistance highly unpredictable. This bottleneck tends to promote genotypes that are resistant to DP. Modelling predicted that the importation of artemisinin-resistant *kelch13* genotypes is likely associated with MDA failure and that the mutants tend to fix in the period immediately following the bottleneck. In settings where there is low importation of *kelch13* mutants, the bottleneck effect is weak and MDA could succeed. According to the model, the best solution to avoid the development of resistance is to improve access to different antimalarials from those used for MDA in the period immediately following MDA in order to eliminate residual resistant parasites (*Nguyen, unpublished report*).

Key conclusions from modelling on the contribution of MDA to malaria elimination and drug resistance:

- Ideally, some preconditions should be met to ensure the usefulness of MDA: excellent case management, effective vector control, low importation, high coverage, and timing during a low transmission period. Nevertheless, in low transmission settings, MDA could compensate for pockets of suboptimal case management if timed correctly, whereas in areas of high transmission, MDA could compensate for poor reactive case detection.
- Overall population coverage of MDA is a key determinant of its impact and simulated effectiveness, whether high coverage is achieved in one or multiple rounds.
- Based on model results, the reduction in transmission from MDA is expected to be greater and longer lasting in lower transmission settings and within smaller populations.
- By deploying case management or other concomitant interventions post-MDA, the low levels of transmission achieved may be maintained.
- To reduce the risk of drug resistance, access to treatment with different antimalarials should be expanded immediately following the MDA – the most sensitive period for selection of resistance.

Mass primaquine preventive treatment (MPPT) as accelerator of P. vivax elimination

Lessons from the past

In the past, several countries aiming for *P. vivax* elimination deployed MPPT regardless of G6PD enzyme activity. The lessons learned from these large-scale MDA operations conducted in Azerbaijan, northern Afghanistan, Tajikistan and the Democratic People's Republic of Korea can help to inform and guide present and future implementation strategies. In these countries, over 8 million people received either a 14-day "standard" or a 17-day "interrupted" PQ treatment to control *P. vivax* malaria epidemics *(30)*.

The drugs were administered to the population by teams who carefully supervised the process and closely monitored for PQ-related severe adverse events *(31)*.

In Azerbaijan, the MPPT campaigns were first implemented from 1971 to 1975 in order to contain and control a *P. vivax* epidemic that occurred in 1970–1972. During the spring of 1971, approximately 90% of the targeted population received a full course of PQ treatment and coverage was maintained between 87% and 93% the following year *(30,32)*. A 60% reduction in malaria incidence was observed compared to the pre-MPPT period, and the reported frequency of adverse effects was very low, despite an overall 15.4% prevalence of G6PD deficiency with major variations from place to place. Following a malaria resurgence in 1979, another MPPT campaign was implemented between 1980 and 1986. By 1982, there had been a 60% reduction in malaria incidence, with no significant further decrease in malaria cases in subsequent years *(31)*.

Following the experience in Azerbaijan, MPPT was also deployed in North Afghanistan in 1972 and 1973. In this case, 14 villages were targeted with an overall coverage of around 90%. During the next malaria transmission season, the incidence of malaria was reduced three-fold in the treated population compared to the control villages, and the rate of adverse effects reported was less than 1%, despite variable prevalence of G6PD deficiency in the areas where MPPT was deployed *(33)*.

Following the re-establishment of local malaria transmission in Tajikistan in the 1980s, three MPPT campaigns were deployed in the country between 1983 and 2002. The first campaign was unable to achieve a very high coverage and so resulted in only a modest reduction in malaria transmission *(34)*. Following two additional MPPT campaigns in combination with other interventions, malaria was progressively reduced in the country, and the MPPT campaign in 2002 helped to reduce the malaria burden by around 40% *(35)*.

MPPT was implemented in five provinces of the Democratic People's Republic of Korea in five consecutive years from 2002 to 2006. These campaigns contributed to a significant reduction in *P. vivax* malaria in subsequent years *(36)*. More than 94% coverage was achieved in all the deployed MPPT campaigns, ranging from 94% in 2003 to 98% in 2006 *(31,36)*. G6PD deficiency prevalence in the Democratic People's Republic of Korea was estimated at 0.5–2.9%, and the frequency of side-effects was low with no cases of severe haemolysis reported. Even though the campaigns managed to achieve significant reductions in malaria morbidity and mortality, interruption of transmission was not achieved. Therefore, consistent with what has been observed in other scenarios, this example indicates that elimination is not feasible in the absence of complementary measures to accompany the drug-based campaigns *(31)*.

Based on these historical experiences, high coverage of MPPT in combination with vector control interventions has been, in general, highly effective in decreasing *P. vivax* transmission in temperate areas by preventing relapses. Moreover, tolerability of the drug has been good, with a low frequency of adverse events reported even with heterogeneous levels of G6PD deficiency *(31)*.

WHO recommendations on G6PD testing to support safe use of primaquine as anti-relapse treatment for *P. vivax* malaria

Since its introduction in 1952, PQ has remained highly effective for the treatment of *P. vivax* relapses. Nevertheless, the recommended dosage for safe use of the drug must be adapted to the G6PD status of the patient. However, this status is often unknown, as G6PD testing is not available in most malaria endemic settings *(37)*. Therefore, both the individual and public health threats posed by untreated *P. vivax* relapses and the risk of acute haemolytic anaemia need to be considered when discussing the risks and benefits of PQ anti-relapse therapy.

After a new point-of-care qualitative G6PD test was introduced to the market, WHO convened an ERG to assess the performance of the testing devices appropriate for use in resource-limited settings *(38)*. On this basis, WHO developed recommendations on G6PD testing to facilitate guidance and practical advice for NMCPs to ensure safe administration of PQ for preventing *P. vivax* relapses *(37)*. Currently, a 14-day course of PQ at 0.25–0.5 mg base/kg body weight is recommended daily in all transmission settings to treat *P. vivax* in children and adults known not to be G6PD deficient *(37)*. (Shorter regimens are not currently recommended due to low quality of evidence.) In people with known G6PD deficiency, WHO recommends a weekly dose of 0.75 mg base/kg body weight for eight weeks under close medical supervision. In cases where the G6PD status of the patient is unknown and testing is not available, the decision to prescribe the drug must be based on the assessment of the risks and benefits of adding PQ. Factors such as the relapse rate, the *P. vivax* incidence rate, the G6PD deficiency prevalence variants in the region, or the capacity of the health system to closely monitor potential adverse events should be considered in this context *(37)*.

Key conclusions about the role of MPPT in accelerating *P. vivax* elimination:

- In temperate areas, MPPT, especially in combination with vector control and other preventive measures, has resulted in rapid containment of *P. vivax* epidemics and may have contributed to the interruption of local transmission in low transmission settings.
- Health systems with properly functioning services capable of ensuring directly observed therapy and close monitoring of side-effects are needed for the success of MPPT campaigns.
- There are no data on the implementation of MPPT in tropical and subtropical areas.
- Further research is needed for large-scale chemoprevention of *P. vivax* with anti-hypnozoite drugs in the population that is not eligible for 8-aminoquinolines because of G6PD deficiency.

5. Highlighted knowledge gaps

The participants agreed that, after examining the available evidence, there are still many challenges and knowledge gaps regarding MDA that need to be addressed.

The evidence reviewed showed that islands were the only areas at the lower end of the moderate transmission spectrum (parasite prevalence 10–15%) that sustained the short-term impact of MDA. Additionally, the sustainability of transmission reductions was variable in low transmission settings. Further research is needed to assess how the effectiveness of MDA in accelerating elimination may be affected by parasite importation rates, especially in areas of low transmission intensity but high levels of population movement. In order to study this, new approaches to measuring parasite importation and population movements may be needed, including molecular epidemiological methods.

Additional research is also needed to understand the impact of low-density asymptomatic infections on malaria transmission depending on population-level immunity.

The current review showed that MDA campaigns deployed more recently have produced a longer lasting impact on transmission compared to MDA campaigns conducted in the past, most likely due to the concomitant interventions deployed with the MDA. Therefore, more attention needs to be paid to the other interventions deployed before and after the MDA. More research is needed to understand which interventions combined with MDA can achieve the highest impact and which activities are needed to sustain the effect over a longer period of time in each scenario.

It still needs to be clearly determined the number of MDA rounds and number of years for which these should be implemented in order to achieve levels of transmission low enough to enable implementation of reactive strategies, as well as the level of transmission at which MDA campaigns should stop and be replaced with investigation and clearing of individual cases, management of foci and follow-up.

Additional areas requiring further research include the optimal timing of MDA rounds and the level of coverage that could be defined as “high”, and how best to measure coverage. Another question that still needs to be addressed is how best to maximize adherence to drug regimens.

With the available evidence, it is difficult to separate the synergistic effects on malaria transmission resulting from different interventions deployed at the same time as the MDA, for example, access to treatment, improved vector control and intensified surveillance. Modelling could help to shed light on the relative impact of different interventions, identify the best mix of interventions in different epidemiological scenarios and inform the decision-making process.

Concerns about the safety of ACTs in the early stages of pregnancy were also raised. Even though most field trials have excluded pregnant women in the first trimester, the large-scale deployment of MDA will unintentionally expose women in the early stage of pregnancy to these medicines. The need for more safety data was highlighted. This will require intensified pharmacovigilance and follow-up of pregnant women in the post-MDA period in order to monitor the effect of inadvertent exposure to ACTs in the first trimester.

Given the results of the studies applying MDA to selected high-prevalence villages, more research is needed to define the minimum population size for MDA implementation, considering local transmission dynamics. These studies will inform the best deployment strategies for focal MDA, including the need for synergistic interventions to sustain impact and accelerate elimination.

One of the major research gaps identified was the lack of evidence regarding the impact of MDA on *P. vivax* in tropical areas, which could be addressed through pilot studies, field trials and modelling. The need for more research to expand the safe use of PQ, and also potentially tafenoquine, as part of chemoprevention strategies taking into consideration G6PD deficiency testing was also emphasized. Additionally, research efforts should address whether MDA deployed over multiple years in non-island settings of moderate to high transmission could help to reduce transmission over the long term.

Given that the sustainability of an intervention depends on its comparative cost and effectiveness, more research is needed on the cost-effectiveness of MDA in combination with other interventions. Research should also include analyses of social acceptability and programmatic suitability, as well as the economic costs of updating NMCPs' policies and mobilizing health workers to facilitate deployment of the intervention. Research on community engagement methods would also be needed, as well as studies to ascertain the extent to which MDA also promotes higher treatment-seeking rates and training of community health workers who can provide other health services such as case management.

6. Conclusions and recommendations

General considerations

MDA can play an important role in malaria control and elimination. Regardless of whether the final aim of the strategy is the reduction of morbidity and mortality or reduction of transmission, there are some fundamentals that should always be applied *(5)*:

- High levels of coverage of the eligible population should be achieved to ensure maximum impact.
- MDA should be deployed as a component of a package, in combination with other strategies such as vector control, case management and intensified surveillance.
- Effective pharmacovigilance procedures should be implemented to ensure that the antimalarial medications deployed are safe.
- The community should be engaged at the local, district and national levels to improve acceptance and adherence.
- Post-MDA activities, in particular intensified surveillance and improved access to case management, should be in place to help sustain the gains achieved.

Proposed recommendations

Based on the review of the new evidence generated since 2015, the ERG proposed to update the current WHO recommendations as follows.[9]

Recommendation 1:
Use of MDA to accelerate progress towards elimination (i.e., significant reductions in malaria transmission sustained over time) of *P. falciparum* malaria can be considered in areas of very low to low transmission (parasite prevalence <10%) where there is good access to effective treatment and effective implementation of vector control and surveillance, and limited risk of re-introduction of infection. Additionally, MDA can be considered in small islands (<500 000 population) with moderate transmission (*P. falciparum* parasite prevalence 10–15%) where there is limited risk of re-introduction of parasites, effective treatment, and effective implementation of vector control and surveillance.

There is no evidence that MDA, even in conjunction with other interventions, can interrupt transmission, yet MDA has been shown to rapidly decrease *P. falciparum* prevalence and incidence when deployed in combination with good access to malaria case management, vector control and intensified surveillance. In low transmission areas, several studies have demonstrated sustained reductions after completion of the MDA campaigns. Several factors contributed to sustaining the decreased transmission levels after the MDA campaign, including improved access to malaria case management, optimized vector control, and intensified surveillance and response. Similar factors contributed to sustaining decreased transmission levels in island settings, but it is likely that reduced parasite importation contributed importantly to maintaining the impact of MDA over several years in those settings.

Recommendation 2:
In areas with moderate to high transmission, MDA may produce a short-term reduction in malaria burden, but so far there is no evidence that MDA, with or without additional interventions, will accelerate progress towards elimination. More evidence should be gathered to determine whether repeated rounds of MDA over multiple years in conjunction with other interventions in these settings could sustain reduced transmission and accelerate progress towards elimination.

There is clear evidence that MDA, in combination with enhanced case management, effective vector control and intensified surveillance, reduces *P. falciparum* malaria health outcomes in the first three months post-MDA in moderate transmission settings, but the results from high transmission areas are inconclusive. However, reports from areas of moderate transmission have shown that no areas have managed to sustain those reductions post-MDA, except for island settings. There was interest in the potential impact of multi-year programmes, combining MDA with other post-interventions to sustain post-MDA reductions in moderate, non-island transmission settings.

Recommendation 3:
Mass primaquine prophylactic treatment, requiring pre-seasonal MDA with daily administration of primaquine for two weeks can be considered as a component of *P. vivax* elimination strategies in temperate regions taking into consideration G6PD deficiency. More evidence should be gathered on the use of MDA with anti-hypnozoite medicines to reduce *P. vivax* transmission in tropical and subtropical areas.

[9] Modified from the previous recommendation. New recommendation.

Based on the evidence presented, a significant impact on *P. vivax* transmission has been observed following deployment of mass PQ prophylactic treatment in combination with vector control interventions in temperate regions. Nevertheless, the need for directly observed therapy and close monitoring of acute haemolytic anaemia in people with G6PD deficiency should always be taken into consideration. Two studies noted only a short-term impact of MDA on *P. vivax* in the GMS. There is a pressing need to investigate the potential role of MDA as a component of elimination programmes in tropical and subtropical settings where *P. vivax* relapses are common.

Recommendation 4:
Given the threat of *P. falciparum* multidrug resistance and the WHO call for malaria elimination in the Greater Mekong subregion (GMS), MDA should be considered as a component of accelerated malaria elimination efforts in the GMS where there is good access to effective treatment and effective implementation of vector control and surveillance, and limited risk of re-introduction of infection. However, because of prevalent multidrug resistance in the region, the options are limited for effective antimalarials that can be used in MDA.

Given the declared urgent need to eliminate malaria in the GMS due to the high levels of antimalarial drug resistance, MDA should be considered as a component of malaria elimination strategies, always with close monitoring of drug safety and resistance. Currently, in some parts of the GMS, a limited number of antimalarial medications remain effective and can be used in MDA campaigns.

Recommendation 5:
Use of time-limited MDA to rapidly reduce malaria morbidity and mortality may be considered for epidemic control as part of the initial response, along with the urgent introduction of other interventions.

Not reviewed as part of this ERG

Recommendation 6:
Use of time-limited MDA to reduce malaria morbidity and mortality may be considered in complex emergencies, during exceptional circumstances when the health system is overwhelmed and unable to serve the affected communities.

Not reviewed as part of this ERG

Recommendation 7:
Medicines used for MDA must be of proven efficacy in the implementation area and preferably have a long half-life. WHO recommends that a medicine different from that used for first-line treatment be used for MDA. Programmes should include drug safety monitoring during MDA campaigns. Drug efficacy should be monitored after the campaign to identify potential emergence of resistance to the antimalarial medicines deployed for MDA.

The ERG members raised their concerns about the safety of MDA, particularly in the first trimester of pregnancy, and the potential emergence of drug resistance, recognizing the need to continue monitoring drug safety and efficacy in MDA deployment areas.

Recommendation 8:
WHO supports the need for more research on the optimum methods for implementing MDA programmes, promoting community engagement and compliance with treatment, and evaluating the effectiveness of MDA programmes. Modelling can help guide the optimum method for administering MDA in different epidemiological circumstances and predict its likely impact.

The need for further guidance on research requirements and study designs (i.e., standardization of outcomes and diagnostics used) to generate evidence in a way that would inform policy-making at global and country levels was also highlighted.

7. References

1. WHO malaria terminology. Geneva: World Health Organization; 2016 (WHO/HTM/GMP/2016.6; https://www.who.int/malaria/publications/atoz/malaria-terminology/en/).

2. Webster JP, Molyneux DH, Hotez PJ, Fenwick A. The contribution of mass drug administration to global health: past, present and future. Philos Trans R Soc Lond B Biol Sci. 2014;369(2645):20130434. doi:10.1098/rstb.2013.0434.

3. Mass drug administration for falciparum malaria: a practical field manual. Geneva: World Health Organization; 2017 (https://www.who.int/malaria/publications/atoz/9789241513104/en/).

4. Mass drug administration, mass screening and treatment and focal screening and treatment for malaria. WHO Evidence Review Group meeting report. Geneva: World Health Organization; 2015 (http://www.who.int/malaria/mpac/mpac-sept2015-erg-mda-report.pdf).

5. Global Malaria Programme. The role of mass drug administration, mass screening and treatment, and focal screening and treatment for malaria. Geneva: World Health Organization; 2015 (https://www.who.int/malaria/publications/atoz/role-of-mda-for-malaria.pdf?ua=1).

6. Bosman A, Lindblade KA, Ortega L. Proposed ERG on mass drug administration in moderate transmission areas and complex emergencies. Geneva: World Health Organization; 2018 (https://www.who.int/malaria/mpac/mpac-april2018-erg-mda-moderate-transmission-session6.pdf?ua=1).

7. Poirot E, Skarbinski J, Sinclair D, Kachur SP, Slutsker L, Hwang J. Mass drug administration for malaria. Cochrane Database Syst Rev. 2013;12:CD008846. doi:10.1002/14651858.CD008846.pub2.

8. A framework for malaria elimination. Geneva: World Health Organization; 2017 (https://www.who.int/malaria/publications/atoz/9789241511988/en/).

9. Eisele TP, Bennett A, Silumbe K, Finn TP, Chalwe V, Kamuliwo M, et al. Short-term impact of mass drug administration with dihydroartemisinin plus piperaquine on malaria in Southern Province Zambia: a cluster-randomized controlled trial. J Infect Dis. 2016;214(12):1831–9. doi:10.1093/infdis/jiw416.

10. von Seidlein L, Walraven G, Milligan PJM, Alexander N, Manneh F, Deen JL, et al. The effect of mass administration of sulfadoxine-pyrimethamine combined with artesunate on malaria incidence: a double-blind, community-randomized, placebo-controlled trial in The Gambia. Trans R Soc Trop Med Hyg. 2003;97(2):217–25.

11. Heaton J, McLean A, Swe MMM, Soe K, Indrasuta C, Khant ZS, et al. Speeding up malaria elimination: a cluster randomized controlled trial of mass drug administration in Southeast Myanmar, an area with artemisinin resistance. Oxford: Centre for Tropical Medicine and Global Health; 2017 (https://www.tropicalmedicine.ox.ac.uk/publications/824534).

12. Morris U, Karolinska Institutet, Mahidol Oxford Tropical Medicine Research Unit, RTI International, The President's Malaria Initiative, University of California San Francisco, et al. Effectiveness of mass drug administration for reducing seasonal malaria transmission in Zanzibar (MaDrAZ) [Clinical trial]; 2016–2017 (https://clinicaltrials.gov/ct2/show/NCT02721186).

13. Escudie A, Hamon J, Schneider J. Results of mass antimalarial chemoprophylaxis with a combination of 4-aminoquinoline and 8-aminoquinoline under rural African conditions in the

region of Bobo-Dioulasso (Upper Volta) 1960. Comparative study in a zone treated with DDT and outside this zone. Med Trop. 1962;22(2):268.

14. Roberts JMD. The control of epidemic malaria in the highlands of Western Kenya. Part I. Before the campaign. Am J TropMed Hyg. 1964;67(7):161–8.

15. Molineaux L, Gramiccia G, World Health Organization. The Garki project: research on the epidemiology and control of malaria in the Sudan savanna of West Africa. Geneva: World Health Organization; 1980 (https://www.who.int/iris/handle/10665/40316).

16. Deng C, Huang B, Wang Q, Wu W, Zheng S, Zhang H, et al. Large-scale artemisinin–piperaquine mass drug administration with or without primaquine dramatically reduces malaria in a highly endemic region of Africa. Clin Infect Dis. 2018;67(11):1670–6. doi:10.1093/cid/ciy364.

17. Mwesigwa J, Achan J, Affara M, Wathuo M, Worwui A, Muhommed NI, et al. Mass drug administration with dihydroartemisinin-piperaquine and malaria transmission dynamics in The Gambia – a prospective cohort study. Clin Infect Dis. 2018 Oct 10 [Epub ahead of print]. doi:10.1093/cid/ciy870.

18. Landier J, Parker DM, Thu AM, Lwin KM, Delmas G, Nosten FH, et al. Effect of generalised access to early diagnosis and treatment and targeted mass drug administration on Plasmodium falciparum malaria in Eastern Myanmar: an observational study of a regional elimination programme. Lancet. 2018;391(10133):1916–26. doi:10.1016/S0140-6736(18)30792-X.

19. Landier J, Kajeechiwa L, Thwin MM, Parker DM, Chaumeau V, Wiladphaingern J, et al. Safety and effectiveness of mass drug administration to accelerate elimination of artemisinin-resistant falciparum malaria: a pilot trial in four villages of Eastern Myanmar. Wellcome open Res. 2017;2:81. doi:10.12688/wellcomeopenres.12240.1.

20. Parker DM, Landier J, Thu AM, Lwin KM, Delmas G, Nosten FH. Scale up of a Plasmodium falciparum elimination program and surveillance system in Kayin State, Myanmar. Wellcome Open Res. 2017;2:98. doi:10.12688/wellcomeopenres.12741.2.

21. Peto TJ, Tripura R, Davoeung C, Nguon C, Nou S, Heng C, et al. Reflections on a community engagement strategy for mass antimalarial drug administration in Cambodia. Am J Trop Med Hyg. 2018 Jan 20;98(1):100–4. doi:10.4269/ajtmh.17-0428.

22. Adhikari B, Pell C, Phommasone K, Soundala X, Kommarasy P, Pongvongsa T, et al. Elements of effective community engagement: lessons from a targeted malaria elimination study in Lao PDR (Laos). Glob Health Action. 2017;10(1):1366136. doi:10.1080/16549716.2017.1366136.

23. Sahan K, Pell C, Smithuis F, Phyo AK, Maung SM, Indrasuta C, et al. Community engagement and the social context of targeted malaria treatment: a qualitative study in Kayin (Karen) State, Myanmar. Malar J. 2017 Feb;16(1):75. doi:10.1186/s12936-017-1718-y.

24. McLean ARD, Wai HP, Thu AM, Khant ZS, Indrasuta C, Ashley EA, et al. Malaria elimination in remote communities requires integration of malaria control activities into general health care: an observational study and interrupted time series analysis in Myanmar. BMC Med. 2018 Oct;16(1):183. doi:10.1186/s12916-018-1172-x.

25. Carrara VI, Sirilak S, Thonglairuam J, Rojanawatsirivet C, Proux S, Gilbos V, et al. Deployment of early diagnosis and mefloquine-artesunate treatment of falciparum malaria in Thailand: the Tak Malaria Initiative. PLoS Med. 2006 Jun 6;3(6):e183.

26. Brady OJ, Slater HC, Pemberton-Ross P, Wenger E, Maude RJ, Ghani AC, et al. Role of mass drug administration in elimination of Plasmodium falciparum malaria: a consensus modelling study. Lancet Glob Health. 2017;5(7):e680–7. doi:10.1016/S2214-109X(17)30220-6.

27. Gerardin J, Bever CA, Bridenbecker D, Hamainza B, Silumbe K, Miller JM, et al. Effectiveness of reactive case detection for malaria elimination in three archetypical transmission settings: a modelling study. Malar J. 2017 Jun;16(1):248. doi:10.1186/s12936-017-1903-z.

28. Pemberton-Ross P, Chitnis N, Pothin E, Smith TA. A stochastic model for the probability of malaria extinction by mass drug administration. Malar J. 2017;16(1):1–9. doi:10.1186/s12936-017-2010-x.

29. Kaneko A, Taleo G, Kalkoa M, Yamar S, Kobayakawa T, Bjorkman A. Malaria eradication on islands. Lancet. 2000;356:1560–4.

30. Kondrashin AV, Baranova AM, Sergiev VP. Widespread use of primaquine for control of Plasmodium vivax epidemics in a population with varying degrees of G6PD deficiency. Med Parazitol (Mosk). 2010;4:24–8 (in Russian).

31. Kondrashin A, Baranova AM, Ashley EA, Recht J, White NJ, Sergiev VP. Mass primaquine treatment to eliminate vivax malaria: lessons from the past. Malar J. 2014;13(1):51. doi:10.1186/1475-2875-13-51.

32. Lysenko AY. The system of anti malaria measures towards containment of large scale malaria epidemic in Azerbaijan and its efficacy. In: Actual problems of malaria prevention in the USSR. Baku: Ministry of Public Health of the USSR and Ministry of Public Health of Azerbaijan SSR (Soviet Socialist Republic); 1973: 70–7 (in Russian).

33. Polevoi NI, Artem'ev MM, Nushin MK, Iakubi G, Lopukhina NG. Problem of malaria and antimalarial measures in northern Afghanistan. 2. Topographical malariological districting of northern Afghanistan and the restructuring of the system of antimalarial measures. Med Parazitol (Mosk). 1975;44(3):338–44 (in Russian).

34. Efremov SB, Bespyatov VF, Maruzoev KD, Mirzoev KD. Efficacy of case detection in Punj district of Tadjik SSR. In: Actual problems of malaria. Moscow: Ministry of Public Health of the USSR; 1988: 73–9 (in Russian).

35. Aliev SP. Malaria epidemic in Tadjikistan, development of scientifically based measures for malaria prevention and control [dissertation]. Moscow: IM Sechenov Moscow Medical Academy; 2005.

36. Pant SD, Chol KY, Tegegn Y, Mandal PP, Chol RK. Mass primaquine preventive treatment for control of Plasmodium vivax malaria in the Democratic People's Republic of Korea: a country success story. WHO South-East Asia J Public Health. 2014;3(1):75–80. doi:10.4103/2224-3151.206889.

37. Testing for G6PD deficiency for safe use of primaquine in radical cure of P. vivax and P. ovale: policy brief. Geneva: World Health Organization; 2016 (WHO/HTM/GMP/2016.9; https://www.who.int/malaria/publications/atoz/g6pd-testing-pq-radical-cure-vivax/en/).

38. Point-of-care G6PD testing to support safe use of primaquine for the treatment of vivax malaria. Geneva: World Health Organization; 2014 (https://www.who.int/malaria/mpac/mpac-march2015-erg-g6pd.pdf?ua=1).

39. Gerardin J, Bever CA, Bridenbecker D, Hamainza B, Silumbe K, Miller JM, et al. Effectiveness of reactive case detection for malaria elimination in three archetypical transmission settings: a modelling study. Malar J. 2017;16(1):248. doi:10.1186/s12936-017-1903-z.

Annexes

8. Annex 1. List of pre-reads

1.	*Mass drug administration for malaria*		Shah, unpublished report
2.	*Large-scale artemisinin-piperaquine mass drug administration with or without primaquine dramatically reduces malaria in a highly endemic region of Africa*	*(16)*	
3.	*Combined impact of mass drug administration and long-lasting insecticidal nets on malaria in Ngazidja (Grand Comore), Union of the Comoros*		Bacar, unpublished report
4.	*a) Impact of 4 rounds of mass drug administration with dihydroartemisinin-piperaquine implemented in Southern Province Zambia* *b) Summary of long-term follow-up of malaria outcomes 15-months after conclusion of a mass drug administration trial in Southern Province Zambia*		Eisele, unpublished report
5.	*MDA expansion in the context of acceleration of malaria elimination in Zambia*		Busiku, unpublished report
6.	*The Magude Project: impact of a malaria elimination demonstration project in Southern Mozambique*		Galatas, unpublished report
7.	*a) Effectiveness of reactive case detection for malaria elimination in three archetypical transmission settings: a modelling study* *b) Does MDA accelerate elimination timelines in southern Zambia?*	*(39)*	Gerardin, unpublished report
8.	*a) Role of mass drug administration in elimination of Plasmodium falciparum malaria: a consensus modelling study* *b) Resurgence of malaria infection after mass treatment: a simulation study*	*(26)*	Smith, unpublished report
9.	*Modelling the impact of malaria mass drug administration on the development of drug resistance*		Nguyen, unpublished report
10.	*The impact of targeted malaria elimination with drug administrations on falciparum malaria in South-East Asia: a cluster randomized trial*		von Seidlein, unpublished report
11.	*Effect of generalised access to early diagnosis and treatment and targeted mass drug administration on Plasmodium falciparum malaria in Eastern Myanmar: an observational study of a regional elimination programme*	*(18)*	

12.	*Mass drug administration trial in Myanmar – Summary*	McLean, unpublished report
13.	*Defining effective, appropriate, implementable strategies for malaria elimination in military forces in Cambodia: a cluster-randomized controlled clinical trial comparing focused mass drug administration with focused screening and treatment*	Wojnarski, unpublished report
14.	*a) Synergy and timing: a concurrent mass medical campaign predicted to augment indoor residual spraying for malaria*	Elliott, unpublished report
	b) Impact of population based indoor residual spraying in combination with mass drug administration on key malaria indicators in a high transmission setting in North Eastern Uganda	Echodu, unpublished report
15.	*Mass drug administration with dihydroartemisinin-piperaquine and malaria transmission dynamics in The Gambia – a prospective cohort study*	*(17)*
16.	*Mass primaquine treatment to eliminate vivax malaria: lessons from the past*	*(31)*
17.	*Testing for G6PD deficiency for safe use of primaquine in radical cure of P. vivax and P. ovale malaria: policy brief*	*(37)*
18.	*Mass drug administration for malaria: research landscape*	MESA, unpublished report

Annex 2. List of participants

Independent experts

Dr Teun BOUSEMA
Radboud University Medical Center
Radboud
Netherlands

Dr Natashia MORRIS
Health GIS Centre
South African Medical Research Council
Durban
South Africa

Dr Meghna DESAI
Centers for Disease Control and Prevention
Atlanta
USA

Professor Harald NOEDL
Medical University of Vienna
Vienna
Austria

Dr Mikhail EJOV (by teleconference)
Independent Consultant
Ottawa

Canada Professor Christophe ROGIER
Central Direction of Army Health Services
Paris
France

Professor Brian GREENWOOD (Chair)
London School of Hygiene and Tropical Medicine
London
United Kingdom

Dr Larry SLUTSKER
Center for Malaria Control and Elimination
PATH
USA

Professor Ivo MUELLER
Walter & Eliza Hall Institute of Medical Research
Melbourne
Australia

Participants

Dr Pedro AIDE
Centro de Investigação em Saúde de Manhiça
Maputo
Mozambique

Dr Dorothy ECHODU
Pilgrim Africa
Kampala
Uganda

Dr Bacar AFFANE (unable to attend)
Programme de Lutte contre le Paludisme
Ministère de la Santé
Moroni
Comoros

Professor Thomas EISELE
Tulane University
New Orleans
USA
Professor Maciej F. BONI
Pennsylvania State University
University Park, PA
USA

Dr Beatriz GALATAS
Barcelona Institute for Global Health
Barcelona
Spain

Professor Arjen DONDORP
University of Amsterdam
Amsterdam
Netherlands

Dr Jaline GERARDIN
Institute for Disease Modelling
Bellevue
USA

Dr Busiku HAMAINZA
National Malaria Elimination Centre
Lusaka
Zambia

Ms Monica SHAH
Centers for Disease Control and Prevention
Atlanta
USA

Dr Jordi LANDIER
Shoklo Malaria Research Unit
Mahidol-Oxford Tropical Medicine Research Unit
Faculty of Tropical Medicine
Mahidol University, Mae Sot
Thailand

Professor Thomas SMITH
Swiss Tropical and Public Health Institute
Basel
Switzerland

Dr Alistair McLEAN
Myanmar Oxford Clinical Research Unit
Yangon
Myanmar

Professor Jianping SONG
Guangzhou University of Chinese Medicine
Guangzhou
People's Republic of China

Dr John MILLER
PATH/MACEPA
Lusaka
Zambia

Ms Maria TUSELL (Rapporteur)
Barcelona Institute for Global Health
Barcelona
Spain

Dr Julia MWESIGWA
Medical Research Council Unit
Banjul
Gambia

Dr Mariusz WOJNARSKI
Armed Forces Research Institute of Medical Sciences (AFRIMS)
Bangkok
Thailand

Observers

Dr Lawrence BARAT
President's Malaria Initiative/USAID
Washington DC
USA
Dr Scott FILLER
The Global Fund
Geneva
Switzerland

Dr Ingrid CHEN
UCSF Global Health Sciences
San Francisco
USA

Bruno MOONEN
Bill & Melinda Gates Foundation
Seattle
USA

Dr Changsheng DENG
Guangzhou University of Chinese Medicine
Guangdong
People's Republic of China

Dr Timothy WELLS
Medicines for Malaria Venture
Geneva
Switzerland

WHO

Global Malaria Programme

Dr Pedro ALONSO
Director

Dr Andrea BOSMAN
Coordinator
Prevention, Diagnostics and Treatment

Dr Peter OLUMESE
Medical Officer
Prevention, Diagnostics and Treatment

Dr Kimberly Ann LINDBLADE
Team Leader
Elimination

Dr Pascal RINGWALD
Coordinator
Drug Efficacy and Response

Dr Xiao Hong LI
Technical Officer
Elimination

Western Pacific Region

Dr Hiromasa OKAYASU
Coordinator
Malaria, Vector-borne and Parasitic Diseases
Phnom Penh
Cambodia

Annex 3. Proposed questions for the ERG on MDA

Overall statement**: There are multiple use-case scenarios for MDA. This review focuses on the impact of MDA on decreasing transmission and accelerating progress towards elimination. This meeting did not address issues of cost or cost-effectiveness, which may be important considerations for some use-case scenarios.**

In relation to the first objective of the meeting:
To determine the effectiveness of MDA combined with other core interventions in reducing *falciparum* or *vivax* malaria incidence and prevalence in areas of moderate to high transmission, with particular attention to the effects of vector control, case management and intensified surveillance on the effectiveness of MDA, and the length of time over which reduction in malaria transmission is sustained post-MDA.

a. In areas of moderate transmission to high transmission[1], does MDA with antimalarial medicines reduce malaria incidence and/or prevalence in the first three months post-intervention compared to no MDA intervention?

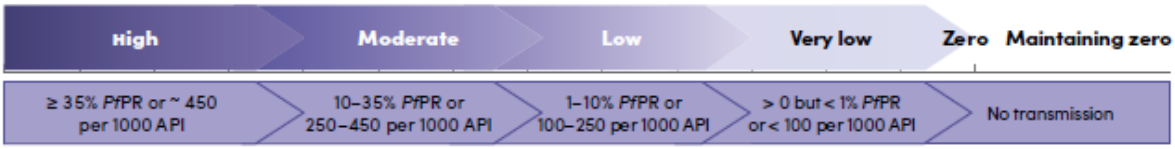
   i. Is there compelling evidence that MDA reduces incidence or prevalence of *P. falciparum* and/or *P. vivax* in the first three months following the last round (e.g., based on comparison to an appropriate contemporaneous control group without MDA, or an interrupted time series analysis with sufficient time points before and after MDA rounds)?

   - **There is no clear evidence that MDA reduces incidence and prevalence of *P. falciparum* in the first three months after MDA in moderate to high transmission settings (*Eisele, unpublished report; Echodu, unpublished report)*.**

   - **No evidence has been presented on the impact of MDA on *P. vivax* in moderate to high transmission settings. Given that incidence and prevalence are generally lower for *P. vivax* than for *P. falciparum,* the number of areas of moderate to high *P. vivax* transmission is limited.**

   ii. What factors were associated with failure or success of MDA in reducing incidence or prevalence of malaria, including coverage achieved during MDA rounds, type of antimalarial medicines used (i.e., short vs. long-acting, two- vs. three-day dosage), addition of primaquine as gametocytocide or anti-relapse therapy, additional interventions implemented during the same period (including case management, vector control, reactive case detection and focal response) and estimated level of parasite importation?

[1] Indicative categories of transmission intensity (from Framework for malaria elimination. Geneva; World Health Organization; 2017)



- **The following factors are associated with the success of MDA in reducing incidence and prevalence:**
    - **The MDA coverage:**
        - **High overall population coverage (>80%) is needed. If the proportion of the population that is not eligible is very high (~15–20%), or if there are substantial subpopulations repeatedly missed by MDA rounds, the impact of MDA will be compromised.**
        - **According to consensus modelling results, the proportion of the population treated in a year is a key determinant of simulated effectiveness, irrespective of whether people are treated through high coverage of a single round or new individuals are reached by implementation of several rounds *(Brady et al., 2017 (26))*.**
    - **The number of rounds:**
        - **There is empirical evidence that multiple rounds per year achieve higher impact than yearly single-round MDA if the additional rounds mean that more people are reached for treatment *(Eisele, unpublished report; Mwesigwa et al., 2018 (17); Brady et al., 2017 (26))*.**
- **There is limited evidence comparing different antimalarial medicines used in MDA and no clear evidence of the advantage of adding a single low dose of primaquine.**
- **There is no clear empirical evidence that the timing of MDA rounds with respect to malaria transmission seasons affects impact, although modelling suggests a greater impact if MDA is done in the dry season or at the end of the rainy season compared to at the beginning of the rainy season (*Brady et al., 2017 (26)*).**

iii. Is the reduction in incidence or prevalence attributed to MDA sufficiently large that the programme could begin intensified surveillance[2] and focal response for malaria elimination? That is, can MDA in this circumstance be considered as an accelerator for malaria elimination?

- **In settings with transmission at the higher end of moderate (>15% parasite prevalence), there is no clear evidence that one to two years of MDA acts as an accelerator towards malaria elimination (i.e., reducing transmission to the level where intensive surveillance and focal response can prevent onward transmission from remaining cases), alone or in combination with other interventions.**
- **In settings with transmission at the lower end of moderate (<15% prevalence), there is some evidence that high coverage of MDA in combination with vector control and case management can reduce transmission to low levels manageable with intensive surveillance and focal response (*Deng et al., 2018 (16); Affane, unpublished report).***
- **In areas of moderate to high transmission, there is a need for more research to determine whether repeated years of MDA could reduce transmission sufficiently to have a sustained impact. This concept is analogous to repeated annual rounds of IRS.**

[2] While the point at which intensified surveillance for elimination can begin depends on caseload and health system capacity, most countries should be able to begin reactive case detection and investigations when cases are few (for example, no more than three malaria cases per week per investigation team). From Malaria surveillance, monitoring and evaluation: a reference manual. Geneva: World Health Organization; 2018 (https://www.who.int/malaria/publications/atoz/9789241565578/en/).

The incremental cost-effectiveness of a multi-year MDA strategy in the context of a package of interventions (i.e., vector control, case management, etc.) should be compared to that of other interventions.

b. In areas of moderate to high transmission where MDA successfully reduced incidence or prevalence in the first three months, was there an increase, decrease or no change in incidence over the following nine months?

   i. Is there compelling evidence that the impact of MDA on reducing the incidence or prevalence of *falciparum* and/or *vivax* malaria can be maintained for up to one year following the last round (e.g., based on comparison to an appropriate contemporaneous control group without MDA, or an interrupted time series analysis with sufficient time points before and after MDA rounds)?

   - **While there is clear evidence that MDA reduces the incidence of *P. falciparum* in the first three months after MDA in areas of moderate to high transmission, there is no compelling evidence of a sustained impact and transmission generally returns to baseline levels rapidly.**

   - **However, in island settings (Comoros) with transmission at the lower end of moderate intensity (i.e., up to 15% prevalence), high coverage of MDA in combination with vector control and case management, and subsequently followed by intensified surveillance, was associated with a large and sustained decrease in malaria prevalence and incidence *(Deng et al., 2018 (16); Affane, unpublished report)*.**

   ii. What factors were associated with failure or success of maintaining reductions in incidence or prevalence of malaria for one year following the last round of MDA, with respect to additional interventions implemented during that period, including vector control intervention, intensified surveillance and focal response, and estimated level of parasite importation?

   - **The factors associated with success in achieving and maintaining a one-year reduction in malaria incidence or prevalence were:**

     - **baseline parasite prevalence in children of up to 15%;**
     - **implementation of intensified surveillance and malaria case management at the community level;**
     - **effective and enhanced vector control with LLINs and/or IRS.**

   Although the level of importation was not well characterized in most studies, limited movement of people in island communities may also have contributed to the sustained low levels of malaria transmission post-MDA in those settings.

c. In areas of moderate to high transmission where MDA successfully reduced incidence or prevalence in at least the first three months, was there evidence that MDA provided selective pressure for emergence of drug resistance, particularly for *P. falciparum*? Does antimalarial MDA increase or decrease the risk of resistance, compared to deployment of the medicine as first-line treatment, considering the reduction in transmission and incidence of clinical cases that follows the MDA intervention?

   - **No new evidence was presented for or against selective pressure for emergence of drug resistance.**

- **Early results from modelling studies indicate that the risk that MDA selects for an increased frequency of resistant strains varies according to the importation of these strains into the MDA area, as well as access to antimalarial medicines that were not used for the MDA regimen in the immediate post-MDA period (*Nguyen, unpublished report)*.**

In relation to the second objective of the meeting:
To review new evidence on the impact of MDA in areas of low to very low transmission in relation to current WHO recommendations on MDA for interrupting *falciparum* malaria transmission in areas approaching elimination.

d. In areas of low to very low transmission has malaria transmission been interrupted following MDA with antimalarial medicines, compared to no MDA intervention?

   i. Is there compelling evidence that MDA interrupts *falciparum* and/or *vivax* malaria transmission in areas with low to very low transmission (e.g., based on comparison to an appropriate contemporaneous control group without MDA, or an interrupted time series analysis with sufficient time points before and after MDA rounds)?

   - **In areas of low transmission, there was no evidence that MDA, even in conjunction with vector control and good case management, can interrupt transmission. However, MDA contributed to decreasing *P. falciparum* transmission to very low levels when deployed in combination with good access to malaria case management, vector control and intensified surveillance, thus accelerating progress towards elimination. This effect was seen particularly in island settings.**

   - **No evidence was presented on the impact of MDA in areas of very low (prevalence <1%) transmission.**

   - **A significant impact on *P. vivax* transmission (lower transmission potential maintained up to six months) has been observed in temperate areas following deployment of primaquine mass prophylactic treatment in combination with other malaria control interventions *(Kondrashin et al., 2014 (31))*.**

e. In areas of low to very low transmission, where *falciparum* and/or *vivax* malaria transmission has been interrupted for up to one year following MDA with ACTs (+/- primaquine), which epidemiological factors and malaria interventions have contributed to maintaining the area malaria-free during this time period?

   - **While there was no evidence of interruption of transmission following MDA in low transmission areas, factors contributing to the maintenance of very low transmission levels achieved with MDA are:**

     - **island settings;**

     - **improved access to malaria case management by increasing the number of community health workers *(Landier et al., 2018 (18); Eisele, unpublished report; McLean, unpublished report)* and thereby decreasing the distance to a malaria treatment provider *(Eisele, unpublished report)*;**

     - **optimized vector control along with the MDA;**

     - **intensified surveillance and response.**

- **According to modelling, in transmission settings with >5% prevalence, infection importation rates represent a very small proportion of the total infections and, therefore, seem to have little effect on the impact of MDA. Nevertheless, with lower prevalence rates, imported cases represent a critical factor that increases transmission (*Brady et al., 2017 (26)*).**

f. For areas of low to very low transmission where interruption of *falciparum* and/or *vivax* malaria transmission has been maintained up to one year post-MDA, what was the coverage of MDA, LLINs and/or IRS, access to treatment and intensified surveillance implemented in the same areas?

- **While there was no evidence of interruption of transmission following MDA in low transmission areas, high coverage levels of MDA, LLINs and/or IRS, together with good access to treatment and intensified surveillance, were implemented in the areas where transmission was maintained at very low levels following MDA.**

g. In areas of very low transmission, is there a level of malaria incidence or prevalence below which antimalarial mass drug administration is no longer considered an appropriate intervention in terms of cost-effectiveness or risk of drug-induced adverse events?

- **No reports on the use of MDA in very low transmission settings were available for review.**

- **In very low transmission settings, the decision to initiate MDA in combination with other interventions should be based on the balance between the risks and benefits of treating the whole eligible population, very few of whom will be at risk of malaria, compared to the cases averted, and the cost-effectiveness of reducing malaria with ongoing interventions.**

Annex 4. Summary of the studies presented

Table 4. Summary of the studies presented

Level of transmission	Country	Parasitaemia pre-MDA (RDT)	Drug used	Number of rounds	Coverage1	Effect seen	Reference
High	Uganda	35% (*Pf*)	DP	4	77%	Decline, seven months sustained (follow-up ongoing)	*Echodu, unpublished*
	Zambia	50.6% (*Pf*)	DP	4	71%[2]	No impact of four rounds of MDA on parasite prevalence in children in the short term	*Eisele, unpublished*
Moderate	Comoros (Anjouan Island)	13.5% (*Pf*)	AP AP + PQ[3]	3	90% (AP) 89% (AP + PQ)	Decline, sustained	*(16)*
	Comoros (Grande Comore)	10.6% (*Pf*)	AP + PQ	2	82% (round 1)[4]	Decline, three years sustained	*Bacar, unpublished*
Low	Mozambique	9.1% (*Pf*)	DP	4	65%	Decline, sustained with concomitant interventions	*Galatas, unpublished*
	Zambia	7.7% (*Pf*)	DP	4	71%	No significant difference between MDA arms and control arms at later time points	*Eisele, unpublished*
	Gambia	<5% (*Pf*)	DP	2	70%	Decline, sustained through the transmission season	*(17)*
	• Myanmar • Viet Nam • Cambodia • Lao PDR	4.1% (*Pf*)	DP + PQ	3	57% completed 3 rounds 14% completed 2 rounds 14% completed 1 round	Decline, with incidence increasing over time, but without returning to baseline levels	*von Seidlein, unpublished*
	Myanmar	5.5% (*Pf*)	DP + PQ	3	60% completed 3 rounds 16% completed 2 rounds 13% completed 1 round	Decline, 20 months sustained (follow-up ongoing)	(18–20)
	Myanmar	2.7% (*Pf/Pv*)	DP + PQ	3	63% completed 3 rounds 16% completed 2 rounds 12% completed 1 round	Decline, three months significantly sustained	*McLean, unpublished*
	Cambodia	10% (*Pf*)	DP + PQ	3	90%	Decline, six months sustained	*Wojnarski, unpublished*

Note: DP: dihydroartemisinin + piperaquine; AP: artemisinin + piperaquine; PQ: primaquine

[1] Average coverage or coverage reporting for consecutive rounds
[2] Overall coverage for high and low transmission households
[3] AP was administered to half of the communities, and the other half received AP + PQ.
[4] Coverage during the second round was not measured.