



**GLOBAL MALARIA
PROGRAMME**



**World Health
Organization**

Evidence Review Group on MDA, MSAT and FSAT

**Malaria Policy Advisory Committee
Geneva, Switzerland
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Chairperson of the Evidence Review Group**

Outline of the Presentation

1. Objectives of the ERG
2. Key questions and methods of work
3. ERG proposed recommendations
4. GRADE Tables
5. Modelling from Malaria Consortium
6. Costing MDA operations

Additional work
completed after
the meeting of
the ERG on MDA

Background

- WHO Technical Consultation held in 2003 concluded there was little evidence that MDA is effective in reducing transmission although a reduction in parasite prevalence and transient reduction in mortality and morbidity were documented in some cases.
- WHO consultation In 2010 reviewed the potential role of MDA to eliminate multi-drug resistance and recommended immediate planning of a pilot MDA operation in western Cambodia or eastern Thailand.
- Cochrane review 2013 concluded that MDA appears to quickly reduce malaria parasitaemia and several clinical outcomes, but more studies are required to assess the impact after 6 months, the barriers for community uptake and the potential contribution to the development of drug resistance.

Rationale for Review

- Renewed interest from countries and funders
- Recent research on MDA and FSAT not all yet in the public domain e.g. FEMSE in Comoros, MDA in Zanzibar, MDA and MSAT in Zambia and MDA at Thai-Myanmar border and Viet Nam.
- Impetus from the crisis of Artemisinin resistance in the Greater Mekong and need to eliminate *P falciparum* there.

Objectives of the ERG on MDA/MSAT/FSAT

1. Review all available published and unpublished reports on the impact of MDA, MSAT and FSAT on malaria transmission.
2. Review results of unpublished studies of MDA and of MSAT/FSAT
3. Evaluate the role of concomitant administration of single low-dose primaquine (PQ)(0.25 mg base/kg) as gametocytocide of *P. falciparum* together with the artemisinin-based combination therapy (ACT) deployed for MDA.
4. Define the specific conditions of application of MDA, MSAT and FSAT to reduce malaria transmission.
5. Identify research gaps

Conclusions - Available Literature

- Overall, MDA reportedly reduced parasite prevalence in the short term in regions of all endemicity, but few studies showed sustained effect beyond 6 months.
- Sustained impact was more often observed in low transmission, highland, or small island settings when combined with additional vector control measures.
- Resurgence sometimes occurred following the intervention (particularly in settings with higher transmission).
- PQ was used with apparent safety for *P. vivax* and *P. falciparum* without G6PD screening, although low reporting of AE may be attributed to limited capacity for pharmacovigilance.

Key Conclusions - MDA in Oncho and Filariasis

- Integrating campaigns into existing programs helped with program roll out due to existing infrastructure.
- Combining MDA with vector control enabled transmission interruption in villages where MDA alone was not sufficient.
- Community engagement was key for LF MDA programme acceptance and achieving a high level of coverage.

Key Conclusions - Ebola in Sierra Leone

- Deploying MDA as an emergency measure to a large population during an Ebola outbreak was feasible and well accepted.
- Selecting the currently used first line drug for MDA reduced the need for retraining CHWs on treatment dosage and administration.
- Success was dependent on joint planning and coordination with partners on a national, district and chiefdom level.
- Social mobilisation through use of media and community engagement was key to disseminating information about the MDA program.

Key Conclusions - Asymptomatic Reservoir Thailand and Vietnam

- MDA combined with PQ, concurrently implemented with vector control in mainland moderate transmission regions resulted in a decrease in parasite carriage, but did not eliminate the transmission reservoir.
- Similarly, efforts to reduce parasite positivity through TME appear to have been constrained by pressure of imported cases from the forest and neighbouring countries.

Key Conclusions - Islands

- Malaria has been eliminated from some isolated islands through the use of MDA, in combination with high coverage with vector-control interventions, a high degree of community involvement, and commitment from political and health authorities. In other instances, such as Comoros, parasite prevalence was reduced but transmission was not interrupted.
- A synergy of methods contributed to success, including vector control, improvements in current control programmes, monitoring of imported cases, effective treatment of infections and mass treatment of the parasite reservoir using PQ.
- Continuing interventions beyond case zero (where no parasites were detected) was key to preventing resurgence and importation of cases in some settings.

Key Conclusions - MPPT for *P vivax*

- MPPT was safely deployed at a large scale with low reporting of AEs in a region with a well-developed primary health-care system and low prevalence of G6PD deficiency.
- Although the number of cases was significantly reduced, it was not possible to interrupt *P. vivax* transmission through the use of MPPT; using vector control might have helped to reach this goal.

Key Conclusions - MSAT and FSAT

- MTAT, MSAT and FSAT achieved modest reductions in malaria transmission in mainland and island settings with low-to-moderate transmission, but did not result in elimination.
- In one FSAT study, targeting of transmission hotspots with LLINs, IRS, larviciding and FSAT reduced parasite prevalence in, but not outside, the hotspots. It was not possible to interrupt transmission in the hotspot using this approach.
- Other FSAT studies were observational and were not designed to evaluate impact on transmission.
- RDTs are not considered sensitive enough to detect all relevant infections for use in MTAT, MSAT and FSAT.
- RACD is a resource-intensive surveillance tool and is unlikely to interrupt transmission

ERG was asked to address these questions

First individually

Should MDA/MSAT/FSAT be recommended **to interrupt transmission**

1. ... and contain the spread of resistance in Thailand/Cambodia?
2.in endemic island communities approaching elimination?
3. in low endemic non-island settings approaching elimination?

..and then in 4 working groups

Should MDA/MSAT/FSAT be recommended **to reduce transmission**

4. ... and reduce morbidity and mortality during malaria epidemics?
5. ... and reduce morbidity and mortality during exceptional circumstances when health services are overwhelmed (e.g. the Ebola outbreak)
6. ... and accelerate progress to elimination in areas with moderate or high transmission?

Proposed recommendations (I)

1. Use of MDA to interrupt transmission of falciparum malaria can be considered in endemic island communities and in low-endemic non-island settings approaching elimination, where there is minimal risk of re-introduction of infection, good access to treatment, and implementation of vector control and surveillance.
2. In view of the growing threat of multidrug resistance and the need to use extreme measures, MDA can be considered as a component of malaria elimination efforts in the Greater Mekong subregion, in areas with good access to treatment, vector control and good surveillance.

Mass drug administration in areas of low malaria prevalence

Patient or population: People living in malaria endemic areas

Settings: Areas with low ($\leq 5\%$) prevalence

Intervention: Mass drug administration (any regimen)

Comparison: Placebo or no intervention (or baseline data in before-and-after studies)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of studies	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	MDA				
Parasite prevalence Study design: Randomized controlled trial Assessed by: Microscopy	1 month		-	1 RCT	-	One cluster-RCT reported zero episodes of parasitaemia throughout five months follow-up in both the control and intervention arms
	-	-				
	6 months					
	-	-				
Parasite prevalence Study design: Uncontrolled before and after study Assessed by: Microscopy	<1 month		RR 0.27 (0.14 to 0.50)	1 study	⊕⊕⊕⊕ very low ^{2,3,4}	One study from a small island, reported a sustained reduction in parasitemia for > 12months following a single round of MDA with CQ
	50 per 1000 ¹	14 per 1000 (7 to 25)				
	12 months		RR 0.02 (0 to 0.12)	1 study	⊕⊕⊕⊕ very low ^{2,3,4}	
	50 per 1000 ¹	1 per 1000 (0 to 6)				
Parasite prevalence Study design: Assessed by: qPCR						
Gametocyte prevalence	-	-	-	1 RCT	-	One cluster-RCT reported zero episodes of gametocytemia throughout five months follow-up in both the control and intervention arms
Development of resistance	Several trials of MDA with pyrimethamine or proguanil monotherapy from the 1950s/60s reported the suspected development of resistance over the first 6 months of MDA.					
Adverse events	The drug related adverse events will depend on the MDA regimen used. Programmatic MDA also has the following risks which have not been quantified: Inadvertently treating pregnant women in their first trimester, Overdose or aspiration in children Contributing to the development of resistance					
The assumed risk has been set at 5%. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).						
CI: Confidence interval; RR: Risk Ratio.						

¹ For illustrative purposes the control group prevalence has been set at 5%.

² Downgrade by 1 for serious risk of bias: This single study is an uncontrolled before and after study, and so at very high risk of confounding.

³ Downgraded by 1 for serious indirectness: This single study from a small island of Taiwan reported the effects of MDA administered as a single dose of chloroquine (12 mg/kg). Further trials are needed from a variety of settings to have confidence in this results.

⁴ Compared to baseline data a large reduction in parasite prevalence was seen at 1 month and 12 months.

Proposed recommendations (II)

3. Use of MDA to rapidly reduce malaria morbidity and mortality can be considered for epidemic control as part of the immediate response, while other interventions are put in place.
4. Use of MDA to reduce malaria morbidity and mortality can be considered during exceptional circumstances, where the health system is overwhelmed and unable to serve the affected communities.

Proposed recommendations (III)

5. There is insufficient evidence to provide guidance on use of MDA in settings with moderate or high transmission; more research is required to inform future recommendations.
6. Using current diagnostic tests, MSAT and FSAT are not suitable as interventions to reduce malaria transmission.

General Considerations 1

- Active engagement of the population at community, district and national levels
- Concomitant deployment of all relevant malaria interventions; in particular, vector control, prompt case management and surveillance;
- Development of a post-intervention strategy to sustain the impact on malaria burden, including a monitoring component to capture potential resurgence
- The capacity to achieve high coverage and adherence at repeated intervals in a coordinated manner.

General considerations 2

- Use Long acting ACTs, preferably not first line
- Add single low dose PQ 0.25mg/kg
- DOT , house to house if possible
- Exclude under 6 months and local recommendations for pregnant women
- Apply in low transmission season
- 3 rounds at monthly intervals
- Need for research modelling on varying approaches in different conditions

What can results from modeling add?

- Limited generalization of field trial results
- Models can explore how MDA effectiveness varies in:
 - Different transmission settings
 - Different MDA programme designs
- Models already extensively validated:
 - Fitted to MDA trial data
 - Predictions constantly tested
- Malaria Modeling Consortium
 - Consensus advice from four leading malaria modeling groups

Imperial College,
London

Swiss TPH,
Basel

IDM,
Seattle

MORU,
Bangkok

Approach taken

Sensitivity of MDA impact to changes from a baseline scenario:

1. Key operational variables analysis

- Coverage, round interval, number of rounds, duration of program

2. Effects in different context

- Endemicity, seasonal timing, population size, imported infections

3. Primaquine analysis

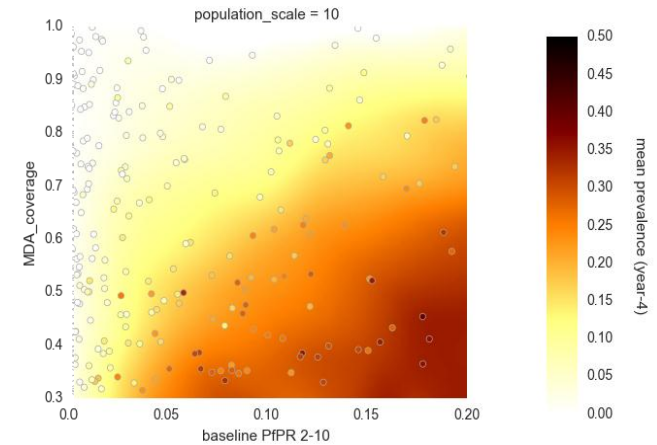
- Presence or absence of low dose primaquine to MDA with long lasting ACTs

Baseline scenario	
Rounds per year	2
Effective coverage	70%
Coverage correlation	1
Round interval	5w
Programme duration	2y
Drug choice	DHA-PQP
Endemicity	5% $PfPR_{2-10}$
Population size	10,000
Seasonality	Zambia-like

Key recommendations

MDA predicted to be effective

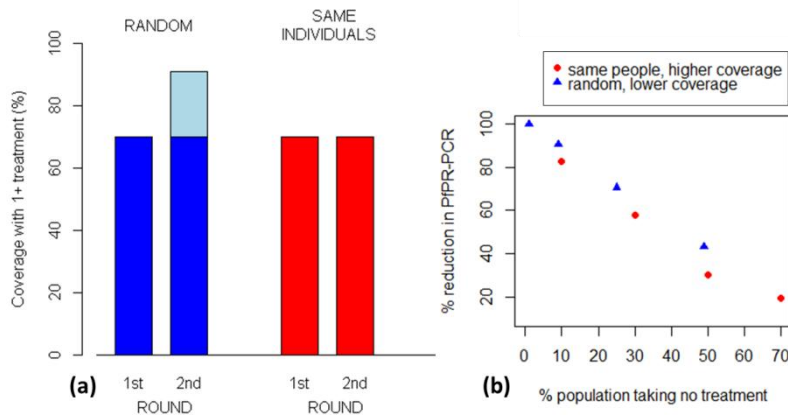
- Suppression will be greater and last longer in low transmission settings



Reaching unique individuals

(maximising the number of people who receive at least one treatment per year), whether it comes from:

- Increasing coverage
- Targeting different people in different rounds
- More rounds



Effect of other factors on MDA impact

Factor	Relative influence on impact
<i>Operational variables</i>	
Increasing effective coverage	High
Decreasing coverage correlation	High
Increasing rounds per year	High (if they reach new individuals)
Decreasing interval between rounds	Low
Increasing duration of programme	Medium
Addition of primaquine	Low
<i>Different contexts</i>	
Optimal seasonal timing of MDA	Medium
Decreasing starting transmission intensity	High
Increasing imported infections	Low
Decreasing population size	High

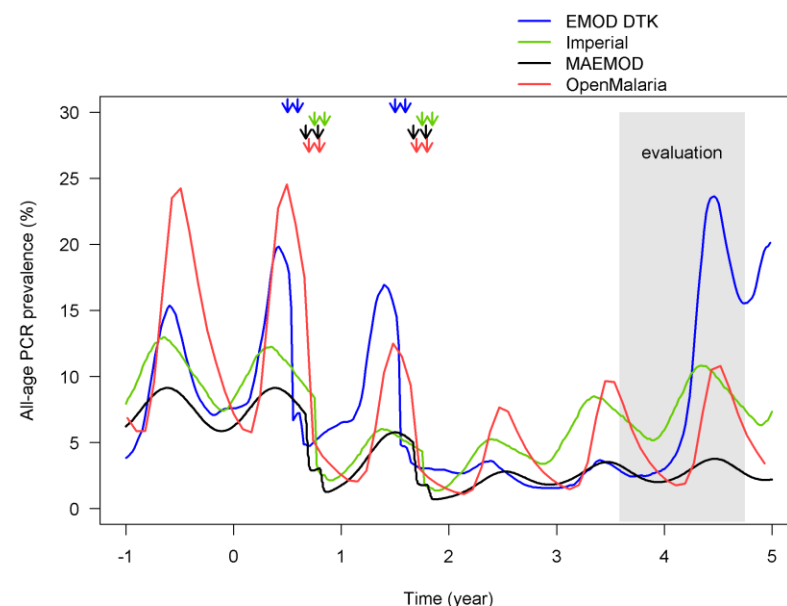
Limitations of these analyses

- Models not fully harmonized

- All show similar patterns, but vary in magnitude of predicted effect
- Can be due to different assumptions, or different interpretations of the baseline
- A full harmonization to understand these differences (like for RTS,S) takes much longer

- Limited ability to predict transmission interruption

- Assumptions about large well mixed populations unrealistic close to elimination



- Models can't tell us everything, but their consensus recommendations provide important evidence

MDA cost analysis

- Cost data were collected for three experiences of using MDA for malaria, all using door-to-door MDA delivery. Two were implemented in island settings (Comoros and Vanuatu) and one in an emergency scenario (Sierra Leone).
- Cost data were available on:
 - drugs, personnel, transportation, supplies, equipment and utilities in Comoros;
 - drugs, local transportation and travel allowances, medical supplies and bednets in Vanuatu; and
 - drugs, other medical supplies, non-medical supplies, personnel, transport, utilities and other recurrent costs in Sierra Leone.
- Covered populations ranged between about 720 people in Vanuatu, 680 000 in Comoros and 3.05 million in Sierra Leone

MDA cost (in 2015 US\$)

Context (year)	District or country	Drug	No of rounds (a)	No of people targeted per round (b)	Coverage rate (c)	No of people covered per round (d)= (b) × (c)	Total cost per round (e)	Total cost per targeted person-round (f)=(e)/(b)	Total cost per covered person-round (g)=(e)/(d)	Delivery cost per targeted person-round	Delivery cost per covered person – round
Island (2007/14)	Comoros	Artequick, PQ	2	679,018	75.5%	515,109	\$ 7.28 million	\$ 10.72	\$ 14.13	\$ 8.38	\$ 11.05
Island (1991)	Vanuatu, Aneityum island	PQ,CQ, SP	9	718	100%	718	n/a	\$ 5.95	\$ 5.95	\$ 4.73	\$ 4.73
Emergency (2014/15)	Sierra Leone, 8 districts	ASAQ	2	3,043,438	92%	2,806,810	\$ 3.32 million	\$ 1.22	\$ 1.31	\$ 0.32	\$ 0.36 (min \$ 0.29–max \$ 0.39)

Figure 1: MDA delivery cost breakdown in Comoros

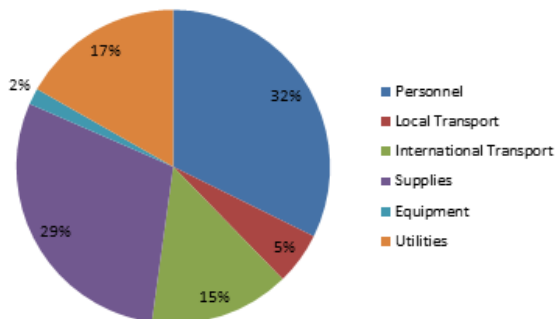


Figure 2: MDA delivery cost breakdown in Vanuatu

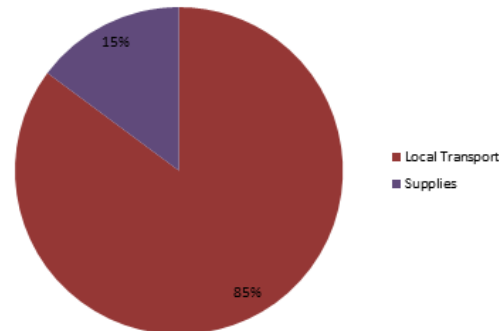
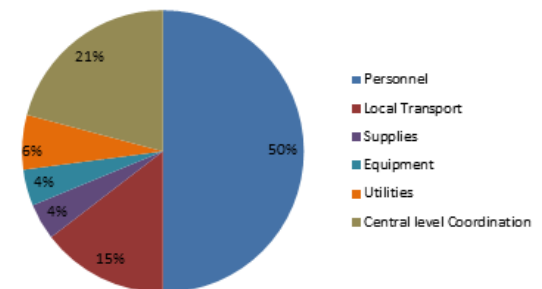


Figure 3: MDA delivery cost breakdown in Sierra Leone (Western areas)



The delivery cost per covered person-round varied greatly : \$ 11.05 in Comoros, \$ 4.73 for all nine rounds (\$ 0.53 per round) in Vanuatu and \$ 0.36 in Sierra Leone.

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