# Proposed ERG on mass drug administration in moderate transmission areas and complex emergencies

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Global **Malaria** Programme

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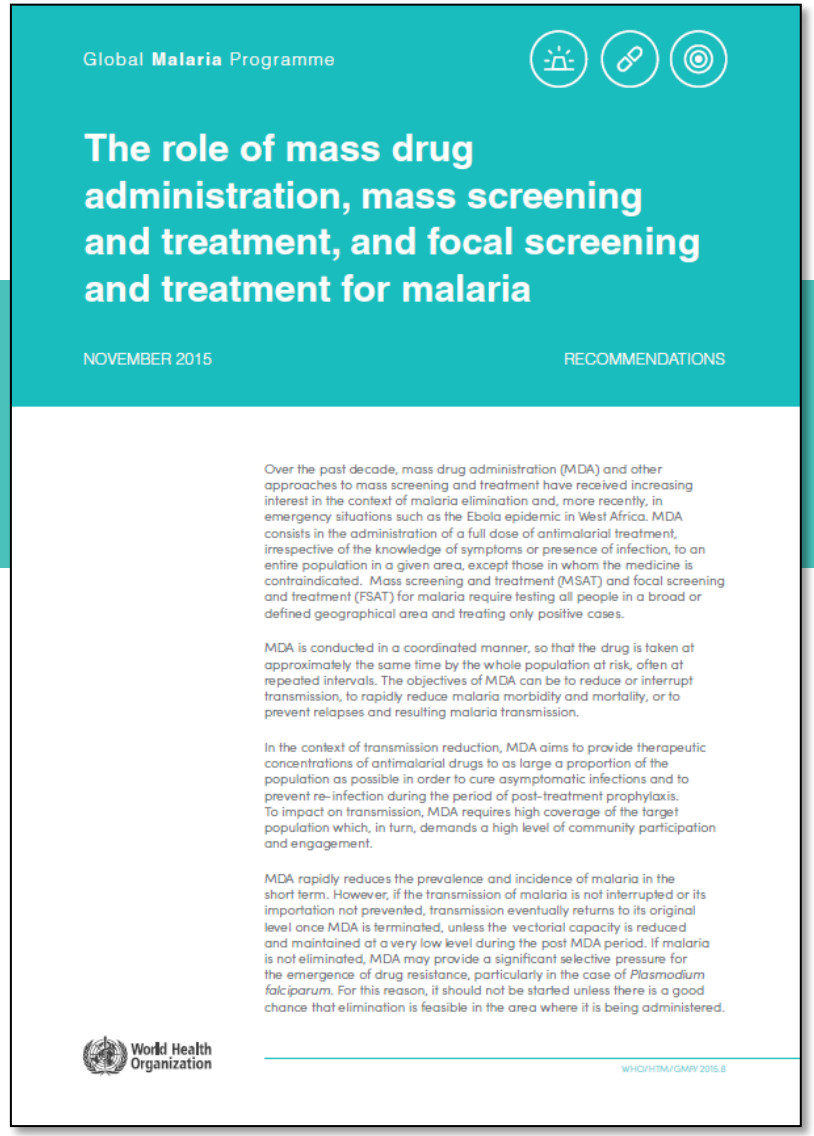
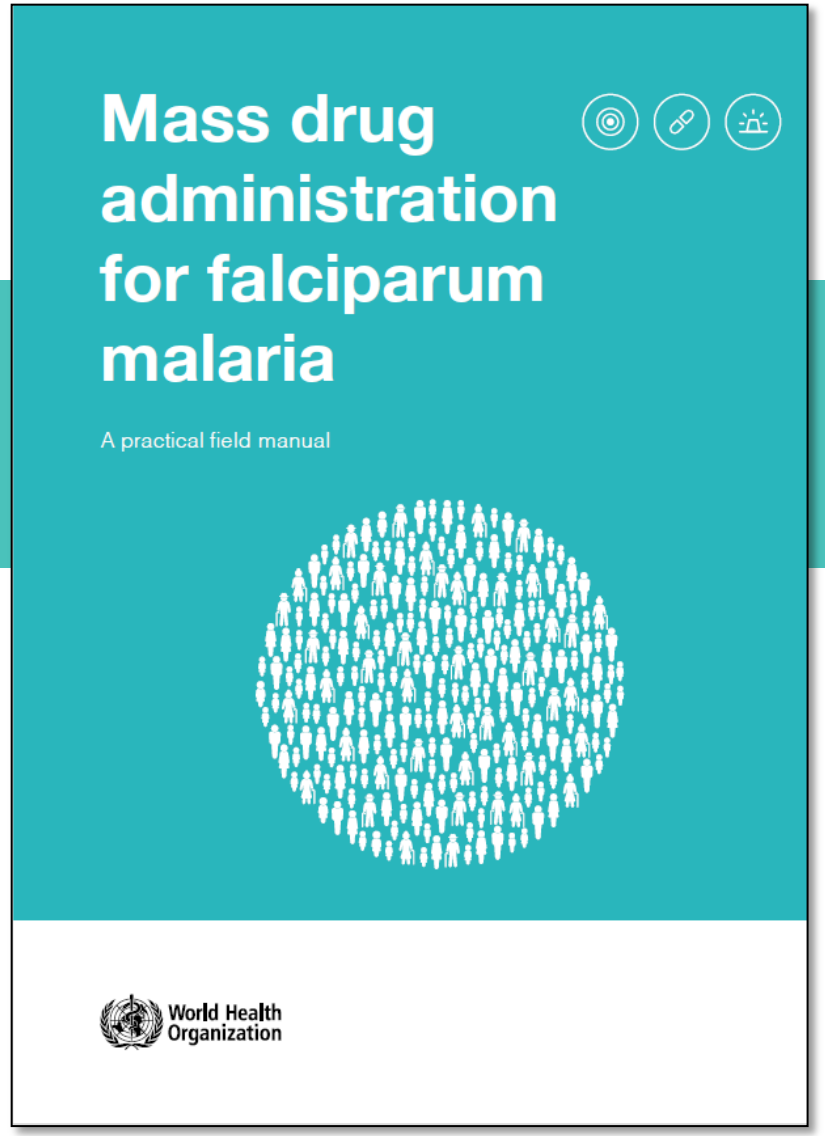
# Outline of the presentation

- Recap of WHO recommendations on MDA and relevant publications
- Basis of WHO recommendations on MDA
- Emerging new evidence on MDA
- Objectives of the ERG
- Preparations and process




http://www.who.int/malaria/publications/atoz/role-of-mda-for-malaria.pdf




http://apps.who.int/iris/bitstream/10665/259367/1/9789241513104-eng.pdf

# WHO recommendations on MDA (I)

Based on a recent evidence review, the WHO Malaria Policy Advisory Committee made the following recommendations on the role of MDA, mass screening and treatment and focal screening and treatment for malaria:

1. Use of MDA for the elimination of *P. falciparum* malaria can be considered in areas approaching interruption of transmission where there is good access to treatment, effective implementation of vector control and surveillance, and a minimal risk of re-introduction of infection.
2. Given the threat of multidrug resistance and the WHO call for malaria elimination in the Greater Mekong subregion (GMS), MDA may be considered as a component of accelerated malaria elimination efforts in areas of the GMS with good access to treatment, vector control and surveillance.

# WHO recommendations on MDA (II)

3. 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.
4. 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.
5. In the absence of sufficient evidence, WHO does not recommend the use of MDA in situations other than for areas approaching elimination, epidemics, and complex emergencies, as specified above (see 1-4) .
6. Mass primaquine prophylactic treatment, requiring pre-seasonal MDA with daily administration of primaquine for two weeks without G6PD testing, is not recommended for the interruption of vivax transmission.

# WHO recommendations on MDA, MSAT and FSAT

7. Mass screening and treatment and focal screening and treatment for malaria are not recommended as interventions to interrupt malaria transmission *(with the tests currently available).*

8. 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. Programs should include monitoring of efficacy, safety and the potential emergence of resistance to the antimalarial medicines deployed for MDA.

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

# Basis of new WHO recommendations on MDA

1. Meeting of WHO Evidence Review Group – April 2015
   http://www.who.int/malaria/mpac/mpac-sept2015-erg-mda-report.pdf

2. GRADE Tables
   http://www.who.int/malaria/mpac/mpac-sept2015-erg-mda-grade-tables.pdf

3. Consensus evidence from Malaria Modelling Consortium
   http://www.who.int/malaria/mpac/mpac-sept2015-consensus-modelling-mda.pdf

4. Review of delivery costs of MDA for malaria
   http://www.who.int/malaria/mpac/mpac-sept2015-cost-data-mda.pdf

5. Review by the Malaria Policy Advisory Committee – Sept 2015
   http://www.who.int/malaria/publications/atoz/mpac-report-september-2015.pdf

**Mass drug administration in areas of low malaria prevalence**

**Patient or population:** People living in malaria endemic areas
**Settings:** Areas with low (≤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 Control | Corresponding risk MDA | | | | |
| **Parasite prevalence**<br>Study design: Randomized controlled trial<br>Assessed by: Microscopy | **1 month**<br>-<br>**6 months**<br>- | <br>-<br><br>- | - | 1 RCT | - | One cluster-RCT reported zero episodes of parasitaemia throughout five months follow-up in both the control and intervention arms |
| **Parasite prevalence**<br>Study design: Uncontrolled before and after study<br>Assessed by: Microscopy | **<1 month**<br>**50 per 1000[1]**<br>**12 months**<br>**50 per 1000[1]** | <br>**14 per 1000** (7 to 25)<br><br>**1 per 1000** (0 to 6) | **RR 0.27** (0.14 to 0.50)<br>**RR 0.02** (0 to 0.12) | 1 study<br>1 study | ⊕⊖⊖⊖ **very low**[2,3,4]<br>⊕⊖⊖⊖ **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 |
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| **Adverse events** | The drug related adverse events will depend on the MDA regimen used.<br>Programmatic MDA also has the following risks which have not been quantified:<br>Inadvertently treating pregnant women in their first trimester,<br>Overdose or aspiration in children<br>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.

Two studies (one uncontrolled before-and-after study and one CRT) were performed in low-transmission settings. The before-and-after study conducted in Taiwan reported a reduction in parasite prevalence at 1 and 12 months following MDA, using a single dose of chloroquine in combination with indoor residual spraying.

[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 singe 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.

**Mass drug administration in areas of high transmission**

**Patient or population:** People living in malaria endemic areas
**Settings:** Areas with high malaria transmission (≥ 40%)
**Intervention:** Mass drug administration (any regimen)
**Comparison:** 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) | Comment |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Control | MDA | | | | |
| **Parasite prevalence**<br>Study design: Cluster-RCT<br>Assessed by: Microscopy | **1 month** | | **RR 0.82**<br>(0.67 to 1.01) | 1 study | ⊕⊕⊖⊖<br>**low**[1,2,3] | |
| | **500 per 1000** | **410 per 1000**<br>(335 to 505) | | | | |
| | **4-6 months** | | **RR 1.16**<br>(0.93 to 1.44) | 1 study | ⊕⊕⊕⊖<br>**moderate**[1,2,13] | |
| | **500 per 1000** | **580 per 1000**<br>(465 to 720) | | | | |
| **Parasite prevalence**<br>Study design: Non-randomized controlled trial<br>Assessed by: Microscopy | **1 month** | | **RR 0.17**<br>(0.10 to 0.28) | 3 studies | ⊕⊕⊕⊖<br>**moderate**[4,5,6,7] | |
| | **500 per 1000** | **85 per 1000**<br>(50 to 140) | | | | |
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A significant reduction in parasite prevalence was seen in the first month after MDA in three non-randomized controlled studies performed in Burkina Faso and Nigeria, and in four uncontrolled before-and-after studies, which also reported a change in parasite prevalence after 3 months. Two uncontrolled before-and-after studies in Cambodia and Palestine showed a sustained reduction in parasite prevalence at 4 months and 12 months, whereas no difference was reported in the Gambian CRT after 1 or 5 months, or in a before-and-after study undertaken in Malaysia after 4–6 months.

Inadvertently treating pregnant women in their first trimester,
Overdose or aspiration in children
Contributing to the development of resistance

The **assumed risk** for parasitaemia prevalence has been set at 50%. Gametocytaemia prevalence was generally lower in the included studies and the **assumed risk** has therefore been set at 10%. The **assumed risk** for parasitaemia incidence is taken from the control group of the single trial. 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.

**Mass drug administration in areas of moderate transmission**

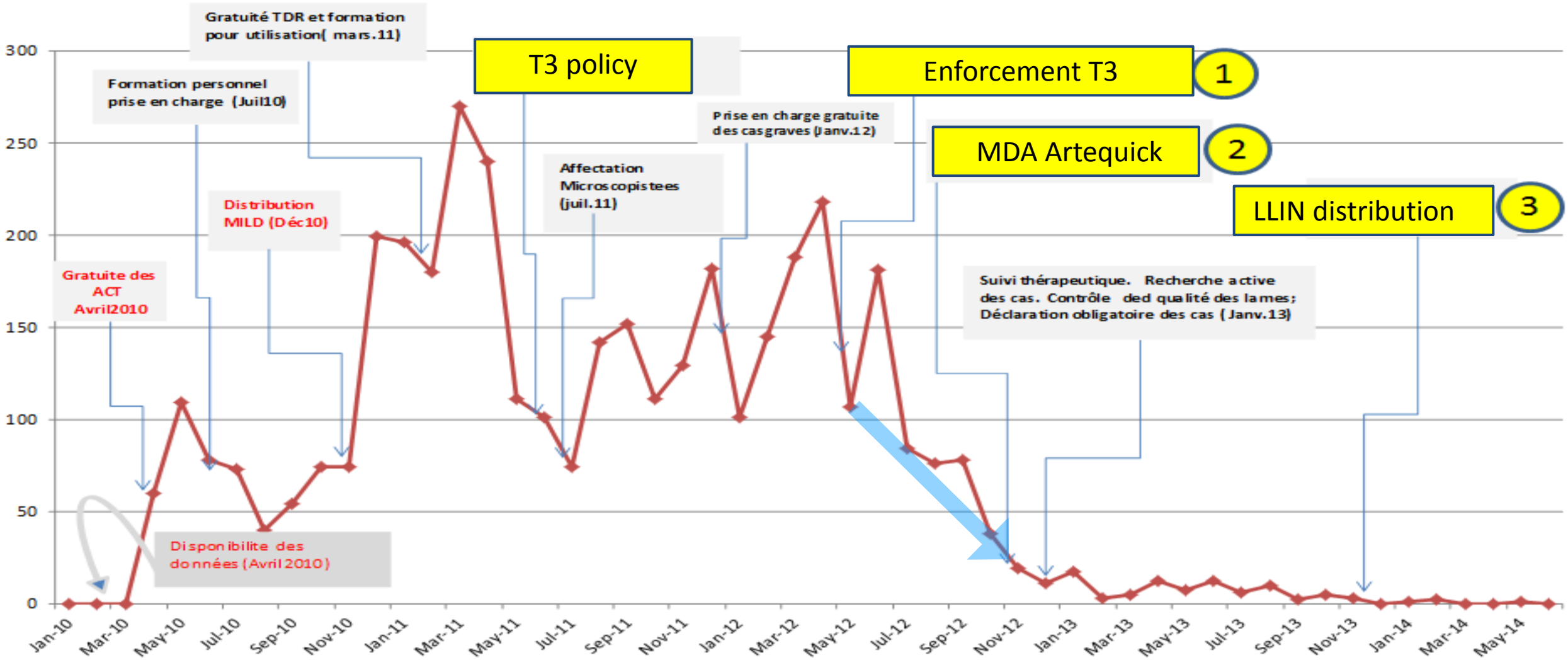
**Patient or population:** People living in malaria endemic areas
**Settings:** Areas with moderate malaria transmission (6-39%)
**Intervention:** Mass drug administration (any regimen)
**Comparison:** No intervention (or baseline data in before-and-after studies)

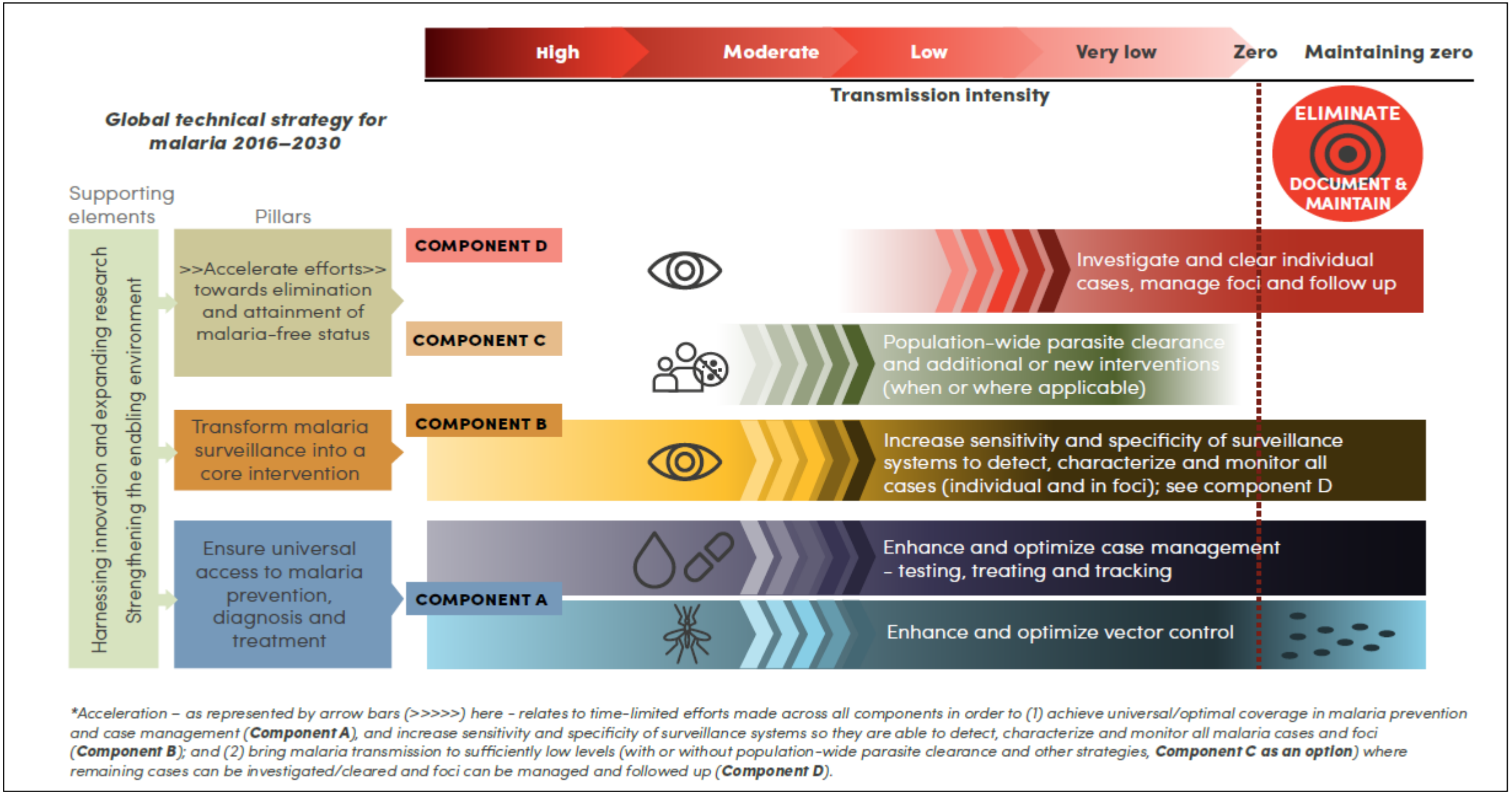
| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of studies | Quality of the evidence (GRADE) | Comment |
|---|---|---|---|---|---|---|
| | Assumed risk Control | Corresponding risk MDA | | | | |
| **Parasite prevalence**<br>Study design: Non-randomized controlled trial<br>Assessed by: Microscopy | **<1 month** | | **RR 0.03** (0.01 to 0.08) | 3 studies | ⊕⊕⊕⊖ **moderate**[1,2,3,4] | MDA probably substantially reduces the prevalence of parasitemia in the first few months after administration (moderate quality evidence) |
| | **250 per 1000** | **5 per 1000** (3 to 15) | | | | |
| | **4-6 months** | | **RR 0.18** (0.10 to 0.33) | 2 studies | ⊕⊕⊖⊖ **low**[1,3,5] | |
| | **250 per 1000** | **70 per 1000** (53 to 95) | | | | |
| **Gametocyte prevalence**<br>Study design: Non-randomized controlled trial<br>Assessed by: Microscopy | **<1 month** | | **RR 0.28** (0.1 to 0.82) | 1 study | ⊕⊖⊖⊖ **very low**[1,6] | There is insufficient evidence to know if, or for how long MDA reduces gametocyte prevalence in these settings |
| | **100 per 1000** | **28 per 1000** (10 to 82) | | | | |
| | **4-6 months** | | **RR 0.52** (0.24 to 1.11) | 1 study | ⊕⊖⊖⊖ **very low**[7] | |
| | **100 per 1000** | **52 per 1000** (24 to 111) | | | | |

In moderate endemic settings in India and Kenya, three non-randomized controlled studies and three uncontrolled studies reported a decrease in parasite prevalence in the first month of follow-up after MDA. At 4–6 months of follow-up, this effect was only sustained in the non-randomized controlled studies. In contrast, the uncontrolled studies indicated either no difference or a higher parasite prevalence compared to the baseline. Addition of larviciding or insecticide-treated mosquito nets (ITNs) resulted in a longer lasting impact.

today with effective anti-malarials.
[5] No serious inconsistency: Consistent and large reductions were seen in these studies.
[4] Upgraded by 1 for large effect size: Very large effects were seen consistently across both controlled and uncontrolled studies.
[5] No serious indirectness: These two studies are both from Kenya in the 1950s, and both administer MDA as pyrimethamine alone. One study continued follow-up for > 6 months when an effect was still present.
[6] Downgraded by 1 for serious indirectness: This single trial in Kenya gave pyrimethamine every six months for three rounds. Different regimens may have different effects and primaquine, a drug with gametocytocidal properties, was not given. One further trial from Nigeria in the 1960s, which only reported on prevalence during an ongoing MDA programme, also administered MDA without primaquine.
[7] Downgraded by 1 for serious indirectness: This single trial found no substantial difference between groups at 4-6 months. Modern trials with different regimens may have different effects. This study did not administer primaquine as part of MDA.

# Malaria reported cases in Anjouan, Comores






**Acceleration – as represented by arrow bars (>>>>>) here - relates to time-limited efforts made across all components in order to (1) achieve universal/optimal coverage in malaria prevention and case management (**Component A**), and increase sensitivity and specificity of surveillance systems so they are able to detect, characterize and monitor all malaria cases and foci (**Component B**); and (2) bring malaria transmission to sufficiently low levels (with or without population-wide parasite clearance and other strategies, **Component C as an option**) where remaining cases can be investigated/cleared and foci can be managed and followed up (**Component D**).*

*A framework for malaria elimination, WHO Geneva, 2017*

# New evidence on MDA for malaria being compiled

- Since the last WHO evidence review on MDA in April 2015, several large-scale trials have been implemented to evaluate the role of MDA combined with other core interventions in accelerating progress towards malaria elimination in areas of moderate transmission. In particular, MDA with artemisinin+piperaquine has been implemented in the Comoros Islands in combination with LLINs, with DHA+piperaquine in the Magude Province of Mozambique together with IRS (pirimiphos-methyl), and with DHA+piperaquine in the Southern Province of Zambia in combination with LLINs. In Mozambique and Zambia, interventions were implemented over two years and results will be published soon.
- Following the successful implementation of MDA with artesunate+amodiaquine (ASAQ) completed in 2015 in Sierra Leone at the peak of the Ebola epidemic, WHO supported an MDA programme to complement vector control and case management in children under 5 in Nigeria's Borno State to rapidly reduce malaria mortality in this population. Four rounds of MDA with ASAQ were implemented from July to November 2017, integrated into polio campaigns. Results are being analysed and will be soon available for review.

# The Cochrane sytematic review is being updated

- The Cochrane systematic review [4] on MDA for malaria included 32 studies in areas with different endemicity, with different medicines and dosages, different timings and number of rounds and concomitant implementation of vector control measures. The review concluded that MDA appears to quickly reduce malaria parasitaemia and several clinical outcomes, but more studies are required to assess its impact after 6 months, the barriers for community uptake and the potential contribution to the development of drug resistance.
- A compilation of the 17 recent studies on MDA for malaria, shared by the Malaria Eradication Scientific Alliance (MESA), is presented in the Annex of the pre-read for MPAC consideration.

4. Poirot et al., Mass drug administration for malaria. Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD008846. DOI: 10.1002/14651858.CD008846.pub2.

# Objectives of the ERG

1. To determine the effectiveness of MDA combined with other core interventions in reducing falciparum malaria incidence and prevalence in areas of moderate 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.

2. 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 malaria transmission in areas approaching elimination and reducing the risk of spread of multi-drug resistance in the Greater Mekong subregion.

3. To review evidence and experience with age-targeted MDA as an intervention to reduce malaria mortality in children exposed to intense transmission and complex emergencies.

# Process for the WHO Technical Consultation

- Three GMP units, Prevention Diagnostics and Treatment together with Elimination and Technical Support and Capacity Building, will collaborate on the technical preparations for the meeting.
- WHO/GMP will convene a group of 12 independent experts in elimination and complex emergencies from national malaria programmes and leading technical agencies, as well as methodology experts in the assessment of data from applied field research.
- Representatives of national malaria programmes and collaborating technical and research institutions (e.g. CDC Atlanta, CISM, Guangzhou University of Traditional Medicine, ISGlobal, LSTM, PATH and STPH) will be invited to present results from MDA trials in areas of moderate transmission and complex emergencies, as well as systematic reviews on MDA in areas with different levels of transmission.
- The ERG meeting will involve up to 25 participants and will require 2 days: 24–25 Sept 2018 proposed as tentative dates.

# Discussion