Draft recommendation: Consider using MDA as an additional tool for the elimination of malaria in low prevalence island or non-island settings where the risk of imported malaria is low

Balance of desirable and undesirable effects

Desirable	Undesirable
There is insufficient evidence from well conducted trials to know if MDA will have a substantial effect on light microscopy parasite prevalence in low prevalence settings (very low quality evidence). Unpublished studies using qPCR suggest there is a reservoir of asymptomatic parasitemia which can sustain trainsmission, and may be reduced through MDA, but these data have not been formally appraised or synthesised.	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

Are the resources required relatively small?

No	*Probably not*	*Uncertain*	*Probably*	*Yes*
☑	☐	☐	☐	☐

The panel did not consider economic data, but considered MDA likely to require substantial resources

Is the intervention feasible to implement?

No	*Probably not*	*Uncertain*	*Probably*	*Yes*
☐	☐	☐	☑	☐

Feasibility has been demonstrated in multiple programs in multiple settings, and is likely to be influenced by the dosing regimen, number of rounds required, and setting

Is the option acceptable to key stakeholders?

No	*Probably not*	*Uncertain*	*Probably*	*Yes*
☐	☐	☑	☐	☐

The panel was uncertain how populations at low risk of malaria would value/accept MDA, especially over prolonged rounds

Overall quality of evidence across all critical outcomes

High	Moderate	Low	Very low
			Very Low

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
	Conditional			

Panel discussion

The panel noted that some countries have successfully eliminated malaria without the use of MDA, using only vector control, prompt treatment and active surveillance.

However, after consideration of the evidence from studies using qPCR the panel recommends MDA as an additional tool to be considered in suitable settings, such as islands, or other communities where the risk of re-introduction of malaria is low.

Remarks

Prior to using MDA ensure there is:
- Good access to prompt and effective malaria treatment,
- High coverage of effective vector control measures,
- An active surveillance system is in place.

Draft recommendation: Consider using MDA as a component of malaria elimination and multi-drug resistance containment efforts in the Greater Mekong Sub-region (GMS)

Balance of desirable and undesirable effects

Desirable	Undesirable
There is insufficient evidence from well conducted trials to know if MDA will have a substantial effect on light microscopy parasite prevalence in low prevalence settings (very low quality evidence). Unpublished studies using qPCR suggest there is a reservoir of asymptomatic parasitemia which can sustain trainsmission, and can be reduced through MDA, but these data have not been formally appraised or synthesised.	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

Are the resources required relatively small?

No	*Probably not*	*Uncertain*	*Probably*	*Yes*
☑	☐	☐	☐	☐

Economic data was not evaluated by the panel, but MDA is likely to require considerable resources

Is the intervention feasible to implement?

No	*Probably not*	*Uncertain*	*Probably*	*Yes*
☐	☐	☐	☑	☐

Feasibility has been demonstrated in multiple programs in multiple settings, and is likely to be influenced by the dosing regimen, number of rounds required, and setting

Is the option acceptable to key stakeholders?

No	*Probably not*	*Uncertain*	*Probably*	*Yes*
☐	☐	☑	☐	☐

The panel was uncertain how populations at low risk of malaria, in settings with resistance would value/accept MDA, especially over multiple rounds/years

Overall quality of evidence across all critical outcomes

High	Moderate	Low	Very low
			Very Low

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
	Conditional			

Panel discussion

The panel considers the development and spread of multi-drug resistance in the Greater Mekong Sub-region an emergency which threatens progress in malaria control worldwide, and considers malaria elimination as the only strategy capable of halting the spread of resistance

The objective of MDA in this setting is rapid reduction in parasite burden, including the asymptomatic reservoir which may be harbouring multi-drug resistant parasites.

Remarks

Prior to using MDA ensure there is:
- Good access to prompt and effective malaria treatment,
- High coverage of effective vector control measures,
- An active surveillance system is in place.

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	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.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[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.

Draft recommendation: There is insufficient evidence to provide guidance on use of MDA to achieve elimination in moderate or high transmission settings.

Balance of desirable and undesirable effects

Desirable	Undesirable
MDA probably substantially reduces the prevalence of parasitemia in the first few months after administration (moderate quality evidence) The longest follow-up from studies in these settings was 4-6 months. At this time point, the prevalence of parasitaemia had risen towards baseline but remained substantially lower than controls in moderate transmission settings (low quality evidence), but had reached baseline levels in high transmission settings (moderate quality evidence).	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

Are the resources required relatively small?

No	*Probably not*	*Uncertain*	*Probably*	*Yes*
☑	☐	☐	☐	☐

Economic data was not evaluated by the panel, but MDA is likely to require considerable resources

Is the intervention feasible to implement?

No	*Probably not*	*Uncertain*	*Probably*	*Yes*
☐	☐	☐	☐	☑

Feasibility has been demonstrated in multiple programs in multiple settings, and is likely to be influenced by the dosing regimen, number of rounds required, and setting

Is the option acceptable to key stakeholders?

No	*Probably not*	*Uncertain*	*Probably*	*Yes*
☐	☐	☐	☑	☐

The panel considered that in moderate to high prevalence settings communities would probably value/accept MDA. No evidence was considered

Overall quality of evidence across all critical outcomes

High	Moderate	Low	Very low
		Low	

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
		No recommendation		

Panel discussion

The panel felt there was insufficient evidence to recommend widespread use of MDA in moderate transmission settings, as the effects are not sustained long-term.

However, the panel could describe specific situations of moderate or high transmission, such as small geographic areas or communities where MDA might be considered and has been used as part of well formulated strategy to move towards elimination.

Remarks

Further research is necessary to define the role of MDA in settings with moderate or high transmission

Draft recommendation: Consider using MDA to rapidly reduce malaria transmission, and reduce morbidity and mortality during outbreaks (once the malaria epidemic has been confirmed).

Balance of desirable and undesirable effects

Desirable	Undesirable
MDA probably substantially reduces the prevalence of parasitemia in the first few months after administration (moderate quality evidence) The longest follow-up from studies in these settings was 4-6 months. At this time point, the prevalence of parasitaemia had risen towards baseline but remained substantially lower than controls in moderate transmission settings (low quality evidence), but had reached baseline levels in high transmission settings (moderate quality evidence).	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

Are the resources required relatively small?

No	*Probably not*	*Uncertain*	*Probably*	*Yes*
☐	☐	☐	☑	☐

Economic data was not evaluated by the panel, but the panel considered MDA to be more affordable than alternatives such as IRS in this scenario.

Is the intervention feasible to implement?

No	*Probably not*	*Uncertain*	*Probably*	*Yes*
☐	☐	☐	☐	☑

The panel considered MDA more feasible than alternative strategies such as IRS, and feasibility has been demonstrated in multiple settings

Is the option acceptable to key stakeholders?

No	*Probably not*	*Uncertain*	*Probably*	*Yes*
☐	☐	☐	☐	☑

The panel considered that in an epidemic, MDA would be acceptable to stakeholders. No evidence was considered.

Overall quality of evidence across all critical outcomes

High	Moderate	Low	Very low
	Moderate		

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
	Conditional			

Panel discussion

Although studies specifically from epidemics were not formally synthesized and presented, the panel was confident that the evidence from moderate/high transmission settings could be applied to epidemics.

The panel considered it likely that MDA could have substantial short term effects on parasite prevalence and contribute to controlling the epidemic.

Remarks

Draft recommendation: Consider using MDA to reduce malaria morbidity and mortality during exceptional circumstances where the health system is overwhelmed and unable to serve the affected communities.

Balance of desirable and undesirable effects

Desirable	Undesirable
MDA probably substantially reduces the prevalence of parasitemia in the first few months after administration (moderate quality evidence) The longest follow-up from studies in these settings was 4-6 months. At this time point, the prevalence of parasitaemia had risen towards baseline but remained substantially lower than controls in moderate transmission settings (low quality evidence), but had reached baseline levels in high transmission settings (moderate quality evidence). Preliminary results from an MDA intervention during the ebola epidemic in Sierra Leone suggest a reduction in rapid diagnostic test (RDT) positivity and the number of calls to the Ebola hotline.	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

Are the resources required relatively small?

No	*Probably not*	*Uncertain*	*Probably*	*Yes*
☐	☐	☑	☐	☐

Economic data was not evaluated by the panel, but the panel considered the cost of MDA to be lower than alternative strategies

Is the intervention feasible to implement?

No	*Probably not*	*Uncertain*	*Probably*	*Yes*
☐	☐	☐	☑	☐

The panel considered the case study from the Ebola epidemic in Sierra Leone where MDA achieved 85% coverage of 2.5 million people

Is the option acceptable to key stakeholders?

No	*Probably not*	*Uncertain*	*Probably*	*Yes*
☐	☐	☐	☑	☐

Full compliance with ASAQ was estimated at just 52% in Sierra Leone. The panel considered alternative regimens may be more acceptable.

Overall quality of evidence across all critical outcomes

High	Moderate	Low	Very low
		Low	

Strength of recommendation

For intervention		No recommendation	Against intervention	
Strong	Conditional		Conditional	Strong
	Conditional			

Panel discussion

The panel considered the unpublished evidence from the Ebola epidemic in Sierra Leone where MDA was deployed to reduce the number of non-Ebola febrile illnesses.

The panel considered MDA for malaria could be deployed as a temporary measure in complex emergencies, in the event that the health system is overwhelmed and unable to reach and serve the affected communities.

Remarks

- In Sierra Leone, Long-lasting Insecticide Treated Bed-nets were also distributed.
- The choice of drug regimen is likely to influence stakeholder acceptance

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	Corresponding risk				
	Control	MDA				
Parasite prevalence Study design: Non-randomized controlled trial 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 Study design: Non-randomized controlled trial 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)				
Development of drug 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** for parasitaemia prevalence has been set at 25%. Gametocytaemia prevalence was generally lower in the included studies and the **assumed risk** has therefore been set at 10%. 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.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] No serious risk of bias: Although there were some differences in prevalence at baseline, these were much smaller in size than the large effects seen post-intervention.
[2] No serious indirectness: These three studies were conducted in Kenya in 1953 and 1954 (pyrimethamine administered every six months for three rounds), and in India in 1953 (amodiaquine administered every two weeks for five rounds). A fourth study from Nigeria in 1973 reported a similar reduction in prevalence during an ongoing MDA program. Although these studies are old, similar effects might be expected today with effective anti-malarials.
[3] 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.

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 Study design: Cluster-RCT Assessed by: Microscopy	**1 month**		**RR 0.82** (0.67 to 1.01)	1 study	⊕⊕⊖⊖ **low**[1,2,3]	
	500 per 1000	**410 per 1000** (335 to 505)				
	4-6 months		**RR 1.16** (0.93 to 1.44)	1 study	⊕⊕⊕⊖ **moderate**[1,2,13]	
	500 per 1000	**580 per 1000** (465 to 720)				
Parasite prevalence Study design: Non-randomized controlled trial Assessed by: Microscopy	**1 month**		**RR 0.17** (0.10 to 0.28)	3 studies	⊕⊕⊕⊖ **moderate**[4,5,6,7]	
	500 per 1000	**85 per 1000** (50 to 140)				
	4-6 months		-	0 studies	-	
	-	-				
Gametocyte prevalence Study design: Cluster-RCT Assessed by: Microscopy	**1 month**		-	0 studies	-	
	-	**-**				
	4-6 months		**RR 1.07** (0.62 to 1.85)	1 study	⊕⊕⊖⊖ **low**[1,2,3]	
	100 per 1000	**107 per 1000** (62 to 185)				
Gametocyte prevalence Study design: Non-randomized controlled trial Assessed by: Microscopy	**1 month**		**RR 0.16** (0.08 to 0.30)	3 studies	⊕⊕⊕⊖ **moderate**[4,5,6,7]	
	100 per 1000	**16 per 1000** (8 to 30)				
	4-6 months		-	0 studies	-	
	-	-				
Development of drug 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** 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.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] No serious risk of bias: This cluster-randomized trial was at low risk of bias.
[2] Downgraded by 1 for serious indirectness: This single study from the Gambia in 1999 administered MDA as AS+SP. The findings may not be easily generalized to other settings, or to alternative MDA regimens. The first time point measured post-MDA was 1-3 months.
[3] Downgraded by 1 for serious imprecision: The result was not statistically significant but the 95% CI is wide and includes important effects.
[4] No serious risk of bias: Although there was some evidence of baseline imbalance between the intervention and control areas, these were generally of smaller magnitude than the effects seen.
[5] No serious indirectness: The data presented here were measured during ongoing multiple-round MDA programmes, not at one month post-intervention. The studies were conducted in Burkina Faso in 1961 (CQ or AQ plus PQ every two to four weeks), and Nigeria in 1975 (SP given every two weeks or every 10 weeks). Although these studies are old, similar effects might be expected today with effective anti-malarials.
[6] No serious inconsistency: The observed effects were consistently large in all three trials.
[7] Upgraded by 1 for the large effect size: Large effects seen in all trials.
[8] No serious risk of bias: These studies are uncontrolled, and so are at very high risk of confounding. However, as the GRADE approach automatically downgrades non-randomized controlled studies by two levels for risk of bias we did not further downgrade.
[9] No serious indirectness: These four studies were conducted in Palestine in 1930 (plasmoquine plus quinine every three weeks for three rounds), Burkina Faso in 1959 (pyrimethamine every two weeks), in Malaysia in 1985 (SP + PQ once only), and Cambodia in 2006 (AS + piperaquine once only plus PQ every 10 days).
[10] No serious inconsistency: Three studies observed large effects, while one small study found no effect.
[11] No serious imprecision: The result is statistically significant.
[12] No serious indirectness: Two large studies found large effects in Burkina Faso in the 1950s (pyrimethamine every 2 weeks for 8 rounds), and Palestine in the 1930s (plasmoquine plus quinine every three weeks for three rounds). One small study from Malaysia in the 1980s found no effect.
[13] No serious imprecision: The 95% CI excludes clinically important reductions at this time point.
[14] No serious inconsistency: The two large studies from Palestine and Cambodia still demonstrated a large reduction at 4-6 months while the small study from Malaysia found no difference
[15] Downgraded by 1 for serious indirectness: Benefits beyond three months have only been demonstrated in this single study from Cambodia. MDA was administered as artesunate plus piperaquine once only followed by primaquine every 10 days for six months.

Studies reporting the suspected development of resistance during MDA

Paper ID	Country	Year	Drug	DOT	Dose	Regimen	Comment
Gaud 1949	Morocco	1948	1. Chloroquine 2. Chloriguane	Yes	Prophylaxis	Weekly for 5 months	Development of resistance to chloriguane suspected as it was less effective than comparator CQ during the second season
Canet 1953	Indochina	1951	1. Paludrine	Unclear	Prophylaxis	Weekly for 18 months	Development of resistance to paludrine suspected at 7-8 months and it was replaced by CQ after 15 months
Schneider 1958a	Cameroon	1956	1. Chloroquine plus pyrimethamine	ND	Prophylaxis	Weekly for 6 months	Development of resistance to pyrimethamine suspected as parasite prevalence initially fell from 67% to 0% but this was not sustained.
Ricosse 1959	Burkina Faso	1959	1. Pyrimethamine	Yes	Prophylaxis	Fortnightly for 4 months	Development of resistance to pyrimethamine suspected as indices returned to a level close to pre-intervention levels in the pyrimethamine group
Van Goor 1950	Indonesia	1949	1. Proguanil 2. Chloroquine	Yes	Treatment	Weekly for 4-10 months	Development of resistance to proguanil suspected as monotherapy with proguanil did not appear to have a sustained impact, and increasing the dose of proguanil did not help.
Gilroy 1952	India	1951	1. Proguanil	Yes	Treatment	Fortnightly for 24 months	Development of resistance to proguanil suspected as the parasite rate rose from 42% to 72% over 6 months of MDA, and proguanil was replaced by chloroquine
Jones 1958	Kenya	1952	1. Pyrimethamine	Yes	Treatment	Every 6 months for 3 rounds	Development of resistance to pyrimethamine suspected as 68 of 221 children (30.7%) had acquired resistant Pf or Pm infections, with resistance observed in larger population as well. (At baseline one child with Pf infection at did not respond to pyrimethamine treatment and showed moderate cross resistance to proguanil).
Archibald 1960	Nigeria	1958	1. Chloroquine plus pyrimethamine 2. Pyrimethamine	Yes	Treatment	Monthly for 7 months	Development of resistance to pyrimethamine suspected as parasite rates reduced to 4.7% after five months of MDA but five months later rates had gone up to nearly as high as baseline
Charles 1962	Ghana	1959	1. Pyrimethamine	No	Treatment	Weekly for 9-12 months	Development of resistance to pyrimethamine suspected as prevalence rate was down to 3.2% by Week 22 but then increased to 25.3% by week 37
Desowitz 1987	Papua New Guinea	1984	1. Chloroquine	ND	Treatment	Multiple MDA efforts over 27 years	Development of resistance to chloroquine suspected as MDA became less effective over 21 years since baseline.