Malaria Policy Advisory Committee Meeting

16–18 September 2015, Geneva, Switzerland
Background document for Session 1

Mass drug administration, mass screening and treatment and focal screening and treatment for malaria

WHO Evidence Review Group meeting report
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Summary

Mass drug administration (MDA) has received renewed interest over the past decade in the context of malaria elimination, as part of multidrug resistance containment and (more recently) in emergency situations such as the West African Ebola outbreak. To develop WHO recommendations, a group of experts met in April 2015 to review recent evidence on the use of MDA, mass screening and treatment (MSAT) and focal screening and treatment (FSAT) in specific epidemiological settings.

The following recommendations were proposed by the WHO evidence review group, for consideration by the WHO Malaria Policy Advisory Committee.

Proposed recommendations

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.
3. Use of MDA to rapidly reduce malaria morbidity and mortality can be consid¬ered 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.
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.

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1 Background

Mass drug administration (MDA) refers to mass treatment of all, or a section of, the population, whether or not symptoms are present. MDA has been implemented by national malaria control programmes (NMCPs) in the past as a way to control epidemics, or to reduce or interrupt transmission, and has generally been used in conjunction with indoor residual spraying (IRS). Based on a review of the results of 19 MDA projects during the period 1932–1999 (1), and a technical consultation held in 2003 (2), WHO concluded that there was little evidence that MDA is effective in reducing transmission, although in some cases a reduction in parasite prevalence and a transient reduction in mortality and morbidity were documented. Therefore, WHO recommended mass treatment of symptomatic patients for epidemic and complex emergency situations, combined with an active search for febrile patients, to ensure that as many cases as possible are treated.

Over the past decade, MDA has received renewed interest, both in the context of malaria elimination initiatives, and as part of efforts to contain multidrug resistance. In 2010, a WHO consultation reviewed the potential role of MDA to eliminate multidrug resistance in the Greater Mekong subregion (GMS), based on evidence of the impact of existing interventions, and operational and modelling considerations (3). The consultation recommended immediate planning of a pilot MDA operation in western Cambodia or eastern Thailand, and the collection of essential information on the safety and efficacy of candidate drugs for MDA.

The 2010 consultation also reviewed the potential role of mass screening and treatment (MSAT), in which all the people in a broad geographical area are screened, regardless of whether they have symptoms of malaria. MSAT generates important information on the epidemiology of malaria, which can be useful for further containment efforts. However, this approach is resource intensive and logistically challenging, especially in view of the lack of field-ready, high-throughput, diagnostic tests that are sensitive enough to detect submicroscopic parasites. When applied in a defined geographical area (sometimes households), the strategy is defined as focal screening and treatment (FSAT), in which everyone is screened, and treatment is provided for those who test positive. FSAT is operationally more feasible than MSAT, but is not delivered simultaneously in the whole of an area sustaining malaria transmission; hence, it is unlikely to contribute significantly to elimination efforts. In 2010, WHO experts concluded that the contribution of MSAT and FSAT in reducing transmission needs to be confirmed (3).

Abbreviations

ACD	active case detection	LAMP	loop-mediated isothermal amplification
ACT	artemisinin-based combination therapy	LF	lymphatic filariasis
AE	adverse event	LLIN	long-lasting insecticidal net
AL	artemether-lumefantrine	MDA	mass drug administration
ASAQ	artesunate-amodiaquine	MPPT	mass primaquine prophylactic treatment
CHW	community health worker	MSAT	mass screening and treatment
CQ	chloroquine	MTAT	mass test and treatment
CRT	cluster randomized trial	NMCP	national malaria control programme
DBS	dried blood spots	nPCR	nested PCR
DHA-PPQ	dihydroartemisinin-piperaquine	NTD	neglected tropical disease
DOT	directly observed therapy	PCR	polymerase chain reaction
ERG	evidence review group	PQ	primaquine
FSAT	focal screening and treatment	PV	pharmacovigilance
G6PD	glucose-6-phosphate dehydrogenase	qPCR	quantitative PCR
GMP	Global Malaria Programme	RACD	reactive case detection
GMS	Greater Mekong subregion	RDT	rapid diagnostic test
HRP2	histidine rich protein-2	SP	sulfadoxine-pyrimethamine
IRS	indoor residual spraying	TME	targeted malaria elimination
ITN	insecticide-treated mosquito net	WHO	World Health Organization

2 Overview

2.1 Rationale

A recent systematic review of MDA includes areas of different endemicity, various medicines and dosages, different timings and number of MDA rounds, and concomitant implementation of vector-control measures (4). The review concluded that MDA appears to quickly reduce malaria parasitaemia and several clinical outcomes, but that 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. A subsequent review of 270 published and unpublished grey literature reports of MDA identified 48 MDA studies with follow-up periods of greater than 6 months, of which 12 showed zero indigenous malaria cases in the target population maintained over 6 months after the end of drug administration (5). The review also identified characteristics of successful MDA campaigns (5). Over recent years, implementation research on MDA and FSAT has been conducted in Cambodia (6, 7) and in other countries, for which only some results are in the public domain. Research in other countries includes fast elimination of malaria through source eradication (FEMSE) in Comoros (8), MDA in Zanzibar, MDA and MSAT in Zambia (9), and MDA at the Myanmar–Thai border and in Viet Nam. These studies were discussed at this meeting. Other articles that report large-scale programmatic use in China (10) and the former Soviet republics (11) have recently been published.

There is growing interest from NMCPs on the potential role of MDA, MSAT and FSAT for malaria elimination. In addition, there is interest on the part of the scientific community and funding agencies for the potential role of MDA in combination with other interventions, not only in elimination settings but also in areas with moderate-to-high transmission (12). New evidence on impact and operational requirements in different epidemiological situations is available from unpublished studies. This evidence provides an opportunity to extract lessons learnt and to define further guidance for policy-makers and research groups that are investing in the evaluation of these interventions.

In view of the situation described above, and the urgency of implementing cost-effective interventions for elimination of multidrug-resistant falciparum malaria, the WHO Global Malaria Programme (GMP) convened an evidence review group (ERG) to evaluate recent studies on the role of MDA, MSAT and FSAT for malaria transmission reduction and elimination.

2.2 Objectives

Specific objectives of the ERG were to:

1. Review all available published and unpublished reports on the impact of MDA, MSAT and FSAT on malaria transmission, building on the recent Cochrane review (4), and a recent qualitative review (5).
2. Review the results of experiences and unpublished studies of large-scale implementation of MDA in Comoros, Sierra Leone, the Myanmar–Thai border, Vanuatu and Viet Nam; and of MSAT and FSAT in Cambodia, Kenya, Zambia and Zanzibar.
3. Evaluate the role of the concomitant administration of single low-dose primaquine (PQ) (0.25 mg base/kg) as a gametocytocide of *Plasmodium falciparum*, together with the artemisinin-based combination therapy (ACT) deployed for MDA.
4. Define the specific conditions for application of MDA, MSAT and FSAT to reduce malaria transmission in terms of endemicity, medicines and dosages, use of diagnostics, timings and number of MDA rounds, concomitant implementation of vector-control measures, best strategies to ensure community uptake and pharmacovigilance (PV).

5. Identify research gaps and provide recommendations on data requirements, study methods and ethical considerations for research groups and policy-makers interested in further evaluating the role of MDA, MSAT and FSAT in reducing malaria transmission.

2.3 Process

Data are presented under the following topics:

1. Cochrane systematic literature review and qualitative reviews on the use of MDA for malaria.
2. Lessons learnt from successful use of MDA for elimination of onchocerciasis and lymphatic filariasis.
3. Use of MDA in the context of complex emergencies.
4. Field application of MDA for malaria elimination in island and mainland settings.
5. Mass PQ prophylactic treatment (MPPT) for P. vivax elimination.
6. Field application of MSAT and FSAT for reducing malaria transmission in low-to-moderate-transmission settings.
7. Operational aspects of MDA, MSTA and FSAT implementation.

3 Evidence reviewed

3.1 Systematic review of MDA for malaria

A comprehensive systematic literature review was performed to assess the impact of antimalarial MDA in previously published studies (4). Thirty-two studies from Africa, Asia, Oceania, and Central and South America met the required eligibility criteria for the review. Those criteria were controlled studies comparing direct MDA to a control or placebo group, or uncontrolled before-and-after studies that administered a full treatment course and reported on one parasitological outcome. Most studies were undertaken during the eradication era, and therefore used monotherapy drug regimens; only three trials deployed ACTs. The 32 studies were of various designs:

- eight were non-randomized control studies
- 22 were uncontrolled before-and-after studies
- two were cluster randomized trials (CRTs).

In addition, 10 studies included a vector-control component. The targeted population ranged from 125 people to 2.3 million people, and the number of rounds of MDA varied from a single round to multiple rounds over a period of up to 2 years. Overall, the quality of evidence was deemed to be very low to moderate. Studies were stratified in terms of malaria endemicity using the following brackets: low (<5%), moderate (6–39%) and high (>40%) parasitaemia in children.

Two studies (one uncontrolled before-and-after study and one CRT) were performed in low-transmission settings. The before-and-after study was conducted on the island of Taiwan; it reported a statistically significant reduction in parasite prevalence at 1 and 12 months following MDA, using a single dose of chloroquine (CQ), in combination with IRS (13).

In moderate endemic settings in India and Kenya, three non-randomized controlled studies (14-16) and three uncontrolled studies (17-19) 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 (20). In contrast, the uncontrolled studies indicated

either no difference (18) or a higher parasite prevalence compared to the baseline (21). Addition of larviciding or insecticide-treated mosquito nets (ITNs) resulted in a longer lasting impact.

Mixed outcomes were reported from studies performed in regions of high endemicity. A significant reduction in parasite prevalence was seen in the first month after MDA in three non-randomized controlled studies performed in Burkina Faso (22, 23), and in four uncontrolled before-and-after studies (6, 24-26), but was not statistically significant in one CRT (27) that was undertaken in the Gambia (27).

Four studies indicated 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 (6, 25) and 12 months (6), whereas no difference was reported in the Gambian CRT after 5 months, or in a before-and-after study undertaken in Malaysia after 4–6 months (24). MDA reportedly had a larger impact on reducing prevalence of *P. falciparum* than of *P. vivax*; not all regimens included an 8-aminoquinoline.

A second review comprised a comprehensive literature review of 270 published and unpublished studies, grey literature reports of programmatic delivery of MDA, and key informant interviews to identify operational and logistical challenges, along with success factors and planning considerations (5). Most of the studies were conducted in Africa, with a before-and-after study design, and aimed to reduce malaria morbidity rather than interrupt transmission. The target size was between 100 and 28 million people, and the study length ranged from 1 day to 9 years. Drug regimens were diverse; they ranged from single treatment dose to weekly chemoprophylactic doses given over a period of several years. A significant proportion incorporated PQ, including two reports representing five countries where PQ was delivered as part of MPPT of *P. vivax* to vast populations (up to 28 million), including individuals deficient in glucose-6-phosphate dehydrogenase (G6PD). A total PQ dosage range of 75–720 mg (across several studies) was used to treat *P. vivax*, and 45–162 mg to treat *P. falciparum*, with minimal adverse events (AEs) recorded. This review provided strong evidence that MDA using PQ was an effective intervention for vivax malaria, especially when used as an outbreak response; in some settings, transmission was interrupted. However, the authors acknowledged that, overall, the quality of the data was poor for many studies, making it difficult to draw solid general conclusions (5).

Interviews revealed features that key informants believed contributed to a successful MDA campaign (5):

- when aiming to disrupt transmission in regions with seasonal malaria, MDA should be implemented just before the beginning of the transmission season;
- treatment should be administered by directly observed therapy (DOT), to ensure high compliance (DOT has been used successfully to administer drugs to large populations);
- drug regimens should include 8-aminoquinolines;
- at least 80% coverage of the target population should be achieved;
- MDA should be delivered through small operational units;
- MDA should be combined with effective vector control; and
- community engagement and good communication are crucial to boost acceptance and participation.

Key conclusions

- Overall, MDA reportedly reduced parasite prevalence in the short term in all regions of endemicity, but few studies showed a sustained effect beyond 6 months.
- A sustained effect was more often observed in low-transmission, highland or small island settings when MDA was 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 a limited capacity for pharmacovigilance may have contributed to low reporting of AEs.

3.2 Lessons learnt from successful use of MDA for elimination of NTDs

MDA has formed the cornerstone of transmission elimination programmes for neglected tropical diseases (NTDs). In 2014, 60 million doses were disseminated to 39 million people for the treatment of onchocerciasis, lymphatic filariasis (LF), trachoma, schistosomiasis and soil-transmitted helminths. This global effort was fuelled by drug donations from multiple pharmaceutical companies.

Ivermectin has been used for twice-yearly MDA at high coverage for elimination of onchocerciasis in the Americas. This campaign has been successful, achieving a 96% reduction in cases in the past 23 years, and a reduction in the number of transmission regions from 13 in 1993 to just two in 2014 (28).

The current strategy for interruption of LF transmission is annual MDA using albendazole and ivermectin at high coverage, for at least 6 years. To ease logistical challenges, LF MDA campaigns were integrated into existing onchocerciasis MDA programmes. Ten-year campaigns in Nigeria reported statistically significant decreases in microfilaremia, antigenemia, mosquito infection rate and mosquito infectivity rate. Transmission was interrupted in five of the 10 sentinel villages; and the other villages maintained low-grade mosquito infection rates of 0.32% (29). LF was later eliminated through use of long-lasting insecticidal nets (LLINs) (30).

Interviews revealed that community engagement played a crucial role in improving the perception and acceptance of LF MDA programmes. About 250 000 local volunteers were deployed as community-directed distributors, each of whom distributed drugs house to house to 100 people.

Key conclusions

- Integrating campaigns into existing programmes helped with programme roll-out because of the existing infrastructure.
- Combining MDA with vector control made it possible to interrupt transmission in villages where MDA alone was not sufficient.
- Community engagement was key for acceptance of the LF MDA programme and for achieving a high level of coverage.

3.3 Use of MDA in the context of emergency situations

Public health emergencies have a major detrimental effect on existing health-care programmes, country infrastructure and supply chains. The 2014–2015 Ebola outbreak provided an example of how malaria case management was affected. The health-care system became overwhelmed because of the number of suspected Ebola patients and a loss of health-care workers; also, there was a reduction in the number of people attending facilities through fear of contagion. Ebola and malaria have similar clinical presentation; therefore, MDA was administered with artesunate-amodiaquine (ASAQ). The goal in this context was a rapid reduction in malaria morbidity and mortality (rather than a long-lasting impact) and a reduction in the number of febrile patients without Ebola presenting to the Ebola Treatment Centre.

In Sierra Leone, LLINs were distributed, followed by two rounds of MDA covering a population of about 2.5 million people during the peak transmission season. Eight districts were targeted; these districts were heavily affected by Ebola, and had high malaria transmission and limited access to routine health services. Infants aged under 6 months, pregnant women in the first trimester and quarantined houses were excluded. The MDA was organized in less than 2 months, and involved over 6000 distributors, mainly health professionals and community health workers. A national task force was established and deployed, and surveys showed that messages about the campaign were disseminated mainly by radio (69%) and through health workers (35.2%).

The NMCP monitored the effect of MDA on malaria-related infection, and on the number of suspected cases admitted at Ebola holding centres, compared to control areas. Eighty-five per cent coverage of the target population was achieved. Preliminary results indicated that rapid diagnostic test (RDT) positivity decreased by 56% and 59% following the first and second rounds of MDA, respectively, and that the number of calls to the Ebola hotline also decreased.

Safety of ASAQ was assessed through household surveys (immediately after MDA) that enquired about emerging signs and symptoms. AE were predominantly mild symptoms such as dizziness, weakness and headache. Full compliance to the drug regimen, assessed through pill counts, was only 52%, reportedly due to fear of side-effects. Operational observations included a need to strengthen PV monitoring systems, and to train community health workers (CHWs) on drug safety.

Key conclusions

- 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 to retrain CHWs on treatment dosage and administration.
- Success depended on joint planning and coordination with partners on a national, district and chiefdom level.
- Social mobilization through use of media and community engagement was key to disseminating information about the MDA programme.

3.4 Field application of MDA in varying mainland and island settings

MDA has been used in different contexts to strive towards elimination and to contain drug-resistant parasites. Several studies were considered.

3.4.1 Mainland

MDA combined with PQ

MDA was deployed to a population of about 6000 in a moderate-transmission setting in Cambodia during 2003–2006, with the objective of reducing or blocking transmission by eliminating falciparum asexual and sexual parasite reservoirs. Three rounds of artemisinin-piperaquine (Artequick™) were combined with 9 mg of PQ, which was given every 10 days for 6 months. Individual G6PD status was not tested, and although some individuals took 25 times too much PQ, no AEs were reported. MDA reduced parasite carriage from 52.3% to 2.6%, and no patent parasites were detected in children in eight out of 27 villages; however, it was not possible to interrupt transmission, and resurgence was observed in some endemic areas (6).

Artemisinin drug resistance

Artemisinin forms the core of therapeutic drug regimens used to treat falciparum malaria. Emergence of multidrug resistance threatens to reverse the progress made with malaria control and elimination. Containment of resistant strains is therefore crucial, and is high on the list of priorities for WHO (31). High prevalence of the K13 gene has been reported in symptomatic patients, but also in asymptomatic carriers with submicroscopic infections living near the Myanmar–Thai border. Attempts were made to eliminate the submicroscopic reservoir in four villages through the use of LLINs, and MDA with dihydroartemisinin-piperaquine (DHA-PPQ) once daily for 3 days, combined with a single low dose of PQ. A sustained reduction in submicroscopic prevalence detected through high-volume polymerase chain reaction (PCR) was not seen for *P. vivax* (this finding was attributed to the use of too low a dose of PQ). Nevertheless, submicroscopic *P. falciparum* decreased from 20% to 0.7% for three out of the four villages when assessed 1 month after the three rounds of MDA (but was not eliminated), while clinical incidence declined to <1.4/100 person-years. The fourth village had low population participation (40%), and therefore did not experience a reduction in cases or parasite prevalence.

Multidrug resistance and re-introduction of disease

Viet Nam has achieved a considerable reduction in malaria cases since 1989, and is aiming for elimination by 2020, but emergence of multidrug-resistant parasites is threatening this effort (32). Targeted malaria elimination (TME), which identifies areas for mass treatment, was piloted in moderate-transmission (20–30%) villages, with the aim of focal elimination. Screening was performed using microscopy, RDT and high-volume quantitative PCR (qPCR) (using 1 ml blood samples) on 50 randomly selected adults, at baseline and once a month, followed by a larger pool of individuals every 2 months. Three rounds of TME using DHA-PPQ and PQ was piloted in six villages in the Binh Phuoc province and four villages in the Ninh Thuan province, in combination with IRS and LLINs. Although parasite positivity by qPCR declined following TME, this effect was not sustained over a 6–9 month period. Malaria rebound was suspected to be due to re-introduction of the disease by forest workers, or by those who had visited Cambodia. This study highlights the need for good understanding of local epidemiology, to identify what is driving transmission and which regions should be targeted for MDA.

Key conclusions

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

3.4.2 Islands

Islands present a unique opportunity for interruption of malaria transmission, since an isolated population can be targeted, with less immediate pressure of introduction of cases from nearby areas than is the case on the mainland. It is thought that malaria can be eliminated on isolated islands using MDA and vector control if there is a high enough level of community participation (33). Evidence from several island studies was reviewed.

Comoros

The number of falciparum malaria cases in various islands of Comoros – Anjouan, Grande Comore and Moheli – declined significantly following a combination of MDA, LLINs and IRS, which were deployed from 2007 to 2014. Populations in each of the islands, of between 37 112 and 338 799 people, were targeted with two or three rounds of MDA; LLINs were distributed to all islands and additional IRS was deployed on Moheli. Treatment using artemisinin-piperaquine (Artequick™) and PQ (9 mg) was given by DOT (excluding pregnant women in the first trimester), just before the transmission season.

MDA was implemented in 2007 in Moheli and in 2012 in Anjouan, with high coverage (86–96%). Case incidence was reduced from 23.57 (per 1000 people) in 2011, to 0.14 in 2014 in Moheli, after deployment of LLINs in 2013, and of IRS in 2011, 2012 and 2013. Similarly, it decreased from 64.29 in 2011 to 0.02 in 2014 in Anjouan, after deployment of LLINs in 2013. Although endemicity in Grande Comore was high before MDA, case incidence decreased from 109.4 in 2011 to 5.47 in 2014, following MDA and LLIN deployment in December 2013. This reduction was found to be sustained when last surveyed in January 2015, despite the lower MDA coverage (65%). These successes were thought to be due to the implementation of a combination of effective and synergistic interventions; that is, use of MDA, LLINs, IRS, systematic testing for malaria before treatment and intensified surveillance.

Aneityum Island, Vanuatu

Malaria was eliminated in Aneityum Island in Vanuatu through multiple efforts. MDA was first implemented in 1991 as part of an integrated control programme using a short-term aggressive approach of 9 weeks of PQ (45 mg per dose), CQ and sulfadoxine-pyrimethamine (SP) (~90% compliance) combined with high coverage of ITNs (0.94 per person). MDA was disseminated to the entire population of about 700 people just before the rainy season. For the long-term strategy, MDA and ITNs were combined with annual re-impregnation of beds nets, use of larvivorous fish and good surveillance. By 1997, both *P. falciparum* and *P. vivax* had been eliminated, but *P. vivax* reappeared in 2002. To combat this, a second round of MDA using PQ (daily 0.25 mg/kg for 14 days) and CQ was deployed to those aged <20 years (who formed the microscopically detectable parasitaemic reservoir), along with dissemination of ITNs. These efforts led to a reduction in cases, with occasional relapses, followed by elimination in 2010. Community engagement was key in preventing re-introduction; local microscopists performed surveillance by passive case detection in the community and by active case detection (ACD) at airports (34).

Key conclusions

- 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.

3.5 MPPT for *P. vivax* elimination

P. vivax presents a challenge for elimination due to the persistence of latent hypnozoites that can only be destroyed following radical treatment with an 8-aminoquinoline, which may induce acute haemolytic anaemia in G6PD-deficient individuals. G6PD-deficiency testing is not widely available and, although concerns have been raised about the safety of using MPPT without first determining G6PD status, the approach has been deployed in various geographical regions with minimal PV systems in place (11).

P. vivax was eliminated in the Democratic People's Republic of Korea during the 1970s, but a resurgence occurred during the late 1990s, which was attributed to natural disasters combined with an economic crisis (11). In 2002, a 5-year MPPT programme was implemented, targeting about 7 million people. Prevalence of G6PD deficiency was reportedly low (0.5–2.9%) (35) within this population, and PQ (15 mg) was administered daily for 14 days by DOT after breakfast, with an evening round to reach those missed in the morning. Coverage of 85–90% was achieved, but pregnant women, children aged under 5 years and patients with chronic disease (36 496 people) were excluded from the study. Side-effects were recorded each day, with headache and epigastric pain most common, and "changed colour of urine" and "black urine" contributing to 1.9% and 0.1% of reported side-effects, respectively. No deaths were reported. The number of cases was reduced from 241 190 in 2002 to 9353 in 2006, but it was not possible to interrupt local transmission (11). The investigators attributed this to the absence of vector-control interventions and the inability to access excluded populations. Researchers speculated that including pregnant women but adopting a different drug regimen might improve treatment coverage and increase the impact of MDA.

Key conclusions

- 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.

3.6 Field application of MSAT and FSAT for controlling or eliminating malaria in low-to-moderate-transmission settings

MSAT is screening of an entire population followed by treating positive individuals, whereas FSAT involves screening all individuals in a defined geographical region, followed by treating those who are positive (36-38). As malaria transmission decreases, it is often concentrated in foci or smaller regions. MSAT and FSAT provide a targeted approach to malaria control, by deploying treatment to the detected populations of parasitaemic individuals, with the aim of reducing the parasite reservoir (31). Since it is widely known that submicroscopic carriers contribute to onward transmission of malaria, these methods rely on the use of highly sensitive detection tests. A series of studies in which variants of MSAT and FSAT were deployed in mainland, island and transmission settings were reviewed.

Zambia

Population-wide mass test and treatment (MTAT) was conducted in 2012 for a population in Southern province, Zambia (9). The aim was to reduce parasite prevalence in children, and the number of confirmed cases, and the MTAT was to be followed by an aggressive ACD strategy to eliminate remaining cases. A randomized controlled trial was conducted, comparing an MTAT group to a control group. Both groups received vector control (ITNs or IRS). In the intervention group, three rounds of MTAT were performed during the dry season, using RDTs for detection and artemether-lumefantrine (AL) for treatment. About 85 000 people were enrolled and about 88% coverage was achieved across three rounds. There was a 17% decrease in confirmed malaria case incidence after the intervention in the MTAT arm compared to the control arm, and 53% lower parasite prevalence in children in the MTAT group after the intervention. Although marginal reductions in malaria burden were achieved, MTAT was considered unlikely to eliminate malaria in this setting. The investigators attributed this to low RDT sensitivity (the test missed up to 50% of infections), only 75% adherence to the full drug course, the short half-life of AL (39) and the lack of effect of AL on mature gametocytes (9)(PQ was not administered).

Zanzibar

Wide-scale use of multiple interventions in Zanzibar has controlled malaria to the pre-elimination stage in situations where transmission is low and seasonal, and occurs in focal areas. Three screening approaches were used, none of which used PQ. In one approach, MSAT was implemented to reduce the asymptomatic parasite reservoir by targeting infection foci, which were identified through the surveillance system Malaria Epidemic Early Detection System. Two rounds of MSAT were applied in identified foci, where households were screened by a histidine rich protein-2 (HRP2) RDT, and positive cases were then treated with ASAQ. Coverage of 64% of a population of 12 000 people was achieved for at least one round. Treatment of RDT-positive individuals did not reduce malaria incidence compared to the control group, but RDT sensitivity was low at 5.6% (compared to qPCR) (40). This was felt to be due to the high abundance of low-density infections (<10 parasites per μL), and to 40% of total infections being non-falciparum species (not captured by the RDT used).

In the second approach, screening was triggered if five cases were reported from a village, or 10 from a shehia (a subdistrict governance region). In 2014, some 11 320 people were screened, which resulted in just 1.5% of individuals testing positive (ranging from 0.8% to 11.8% in different villages).

The third approach involved testing the household members of all symptomatic index cases identified at public health facilities, termed malaria case notification. Out of 11 450 household members tested, 6% were positive, which increased the number of infections treated by 26%. Infections detectable by RDT were found to cluster in the same household as symptomatic infections, and also low-density infections to some extent. Since RDTs do not detect the latter, this restricts their applicability for use in MSAT. Also, although loop-mediated isothermal

amplification (LAMP) offers a more sensitive point-of-care test, it remains considerably more expensive. Due to these drawbacks, presumptive treatment was suggested as a strategy for treating those living in transmission foci or within households where an infection has been confirmed.

Cambodia

FSAT was employed to detect foci of asymptomatic parasite carriers with the objective of containing artemisinin-resistant strains in Pailin, Cambodia. In 10 high-incidence villages LLINs were disseminated and RDTs used to screen febrile and subfebrile individuals. Positive cases were initially treated with atovaquone-proguanil for *P. falciparum* and CQ for *P. vivax* using DOT. At follow-up, PCR-positive participants were treated with the same regimen, plus additional PQ using a single dose of 0.75 mg/kg for falciparum, or 0.5 mg/kg for 14 days for vivax, provided that the participant was not G6PD deficient. Interviews were performed to explore population travel history and assess the risk of spreading resistant parasites. Coverage of 72.6% (from a population of 9537 individuals) was achieved for both years, *P. falciparum* prevalence by PCR was low, at <1% (7), and most infections were asymptomatic; no resistant parasites were found. Although 1.6% of people had plans to cross the border, none were parasitaemic.

The study concluded that FSAT is a useful screening tool to identify asymptomatic carriers (who clustered around confirmed cases), but it was considered too slow to be an elimination tool. Instead, PCR-based FSAT is being considered as an epidemiological tool to provide baseline data before MDA, and to enable short-term and long-term monitoring of the impact of MDA. A mobile laboratory has now been deployed in Cambodia to enable rapid, onsite, sensitive molecular parasite detection.

Kenya

Hotspots are regions of higher than average malaria incidence, and are thought to be responsible for seeding infection to the surrounding area. Infection hotspots were targeted in a region of low seasonal transmission in the Kenyan highlands, with the objective of reducing transmission in the entire focus, and interrupting transmission in the hotspot. Serology and nested PCR (nPCR) were used to identify 10 clusters of high exposure, which had about 20% parasite prevalence by nPCR. Five clusters received the intervention, which comprised LLINs, IRS, weekly larviciding and FSAT. The latter involved screening by RDT, followed by treatment using AL (administered by DOT), in parasite-positive compounds. A total of 93.7% coverage was achieved and, after 6 weeks of the intervention, hotspot nPCR prevalence decreased in all five intervention villages and in two control villages. While this was a significant difference, transmission was not interrupted and there was no significant impact outside the hotspots regions. The investigators felt that population-wide MDA was a more appropriate method for this region (Baidjoe, in preparation).

Indonesia, Namibia, Swaziland and Thailand

Reactive case detection (RACD) is an approach used to identify asymptomatic infections that may be clustered around passively detected index cases picked up through surveillance mechanisms. RACD programmes were implemented in low-transmission regions to move towards elimination in Indonesia, Namibia, Swaziland and Thailand. Here, index cases identified by RDT were reported by mobile phone, which triggered a follow-up session where dried blood spots (DBS) were collected from household members, and neighbours within a 500 m radius. Parasites were detected from DBS by LAMP to enable comparison of detection methods. In Swaziland, about 70% coverage was achieved, and LAMP revealed two to three times the number of infections found by RDT. Closer physical proximity to the index case significantly increased risk of being infected (with other household members of the index case being at highest risk); the risk decreased with increasing distance. It was concluded that RACD is a good surveillance approach for revealing asymptomatic subpatent infections that cluster around

index cases. However, the sensitivity of RDTs was deemed too low to detect these additional infections and, while molecular diagnostic tools have adequate sensitivity, they are not point-of-care diagnostics. The RACD study in Swaziland was not designed to evaluate impact on transmission.

Key conclusions

- 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 owing to the number of cases not detected because they are low-density infections or are not present at the time of visit.

3.7 Operational aspects of MDA, MSAT and FSAT implementation

This section details a number of considerations and challenges common to implementation of MDA, MSAT and FSAT; they include choice of drugs, coverage, logistical aspects and features of successful MDA.

3.7.1 Choice of drugs

In choosing which drugs to use, the following should be taken into consideration:

- Efficacious drugs and an optimal regimen must be deployed.
- Pregnancy testing, active follow-up and inadvertent drug exposures may need to be considered, depending on the chosen drug.
- Drugs should be selected so as to avoid increasing drug resistance, and drug resistance markers should be monitored.
- Concurrent interventions (including those for other pathogens) need to be monitored in the target population before roll-out, to avoid interactions between drugs.

3.7.2 Coverage

Obtaining high intervention coverage is crucial to success. The following present challenges to achieving this:

- Ideally, timing of MDA should be structured when people are at home and can be reached.
- Mobile, migrant and remote populations can be especially hard to target for multiday drug regimes.
- People may be unwilling to take drugs when they feel well and have not been tested.
- People of higher socioeconomic status and young men are generally less likely to comply with MDA.
- Imported cases and recrudescent infections can jeopardize programme impact.

3.7.3 Logistical aspects

Several logistical aspects need to be considered:

- Drug stock-outs, ordering issues or customs delays can all contribute towards delayed roll-out of MDA.
- Community drug distributors need to be incorporated into other programmes after MDA, to avoid problems (there have been reports of volunteers distributing counterfeit drugs following programme completion).
- It is important to involve personnel from the existing health system.

In addition to these challenges, there are ethical concerns that need to be considered. These include obtaining informed consent (in research settings), treating participants respectfully in a culturally sensitive manner, and ensuring that benefits outweigh the risks (this is of particular concern when the disease burden is low). The study population must be selected fairly, ensuring that vulnerable populations are protected, and that participants are aware they have the freedom to refuse or withdraw from the MDA programme without penalty, and that their confidentiality is protected.

3.7.4 Features of successful MDA programmes

A number of features common to successful MDA programmes have been identified:

- Collaboration and information sharing between researchers, policy-makers and the community are crucial.
- Community engagement can be increased by meetings, house-to-house visits, printed media (leaflets, banners and posters), mass media (TV and radio) and inclusion of CHWs and local volunteers. Strategies should be optimized for each site. Also, emphasizing the social value of the campaign to the beneficiaries may improve acceptance.
- Integrating programmes with ongoing community-based schemes and other existing MDA programmes (e.g. those for NTDs) is more logistically feasible than starting from scratch.
- Providing incentives to drug distributors and local health workers involved in supervision or pharmacovigilance can support compliance and coverage.

4 Conclusions and recommendations

4.1 General considerations

Under certain conditions, MDA may play a useful role in malaria control and elimination programmes. However, irrespective of specific applications, some essential elements must always be applied. These elements include:

- active engagement of the population at community, district and national levels, including multisectoral collaboration, if relevant;
- 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, using cost-effective interventions, and including a monitoring component to capture potential resurgence; and
- the capacity to achieve high coverage and, at about the same time, to ensure adherence to treatment in the target population, and to do this at repeated intervals in a coordinated manner.

4.1.1 Medicines for mass administration

In most settings, the drug of choice should be a long-acting ACT. Preferably, this should not be the first-line antimalarial medicine used for treatment of symptomatic malaria in that region (which, for many settings, may be DHA-PPQ or artesunate-mefloquine). The drugs selected must be appropriate for the local situation; therefore, alternatives to long-acting ACTs may be used if effective in the particular setting (e.g. chloroquine is effective in Central America).

The addition of a single low dose (0.25 mg/kg) of PQ is recommended to reduce the transmissibility of *P. falciparum* gametocytes (e.g. to eliminate falciparum malaria or reduce transmission of drug-resistant strains). Excluding PQ does not preclude or invalidate the use of MDA.

Currently, there is limited evidence to suggest that MDA contributes to drug resistance, especially if ACTs are deployed in combination with single-dose PQ. There are concerns, however, that the use of monotherapy for MDA in epidemics could lead to strong selection pressure and emergence of drug-resistant parasites.

4.1.2 Drug delivery methods

Full therapeutic dosage should be used for all MDA, MSAT and FSAT regimens. Completion of treatment is critical; therefore, DOT or a comparable delivery system should be used for administration of all doses, to ensure high adherence. DOT could be performed by local health workers and volunteers to improve acceptability and drug uptake. House-to-house delivery of drugs is preferable to inviting people to participate in a central location. Any other approach that would guarantee high coverage without causing movement of the population may be acceptable.

4.1.3 Exclusion criteria

Local recommendations for treatment of pregnant women should be followed, and infants aged under 6 months (or having a body weight of <5 kg) should be excluded from ACT administration. PQ is contraindicated in pregnant women, lactating women and infants aged under 6 months.

4.1.4 Timing and rounds of MDA

With the exception of an epidemic or complex emergency, it is preferable to implement MDA in the low-transmission season, before the start of the malaria-transmission season. At present, the evidence supports recommending three rounds of MDA at monthly intervals. Further research is required to determine whether two rounds would be sufficient in different situations, or even one round in foci elimination.

4.1.5 Monitoring and evaluation

The impact of MDA should be measured by evaluating changes in reported malaria cases or malaria incidence. Impact on malaria transmission can be monitored by serological surveys or surveys based on molecular tests to detect submicroscopic infections. In elimination settings, other methods (e.g. foci investigations) may be used. In the context of eliminating drug-resistant parasites, molecular monitoring of drug resistance markers is an essential component of surveillance.

Additionally, coverage of target population, adherence to treatment, acceptability (which could be measured in a random sample of the population) and monitoring of concomitant interventions should also be recorded. Enhanced PV is recommended for detection and reporting of AE. Routine monitoring of MDA interventions should include monitoring of concomitant medication, adherence to treatment and medication errors.

4.1.6 Further research required

A number of knowledge gaps were highlighted:

- Modelling exercises are needed to calculate:
- the target coverage;
    - the impact of waning coverage over repeated rounds;
    - the impact of random and non-random refusals during repeated rounds of MDA;
    - the number of rounds and intervals between MDA (in regions of different endemicity); and
    - whether addition of single low-dose PQ adds value to ACT for transmission reduction of *P. falciparum*.
- When and how does MDA affect the development of multidrug resistance?
- What is the risk and impact of re-importation, and what is the definition of risk-containment strategies, including optimal post-elimination surveillance methods?
- Identification of optimal methods to increase compliance and community participation.

4.2 Proposed recommendations

4.2.1 Use of MDA to interrupt transmission low-endemic settings

Recommendation 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.

For elimination of malaria in islands and in mainland areas, MDA should be considered as an option as part of a detailed and costed elimination plan, but only when access to treatment is ensured, and vector control and surveillance are implemented concurrently. In the context of an elimination plan, the role of MDA would be to reduce morbidity, leading to rapid case reduction. In low-transmission settings where there is minimal risk of re-introduction of infection, the role would be to contribute to interruption of transmission. The unit of intervention of MDA should be as small as operationally feasible, to maximize the impact in the target population. The intervention can be targeted spatially or to specific “at risk” groups or foci.

4.2.2 Use of MDA to interrupt transmission and contain resistance in Cambodia and Thailand

Recommendation 2

In view of the threat of spreading multidrug resistance and the need to use extreme measures, MDA can be considered as a component of malaria elimination efforts in the GMS in areas with good access to treatment, vector control and good surveillance.

At the Cambodia–Thailand border, *P. falciparum* has become resistant to almost all available antimalarial medicines, threatening progress achieved in this region to date. If not contained, this resistance could lead to a rise in the disease burden in other parts of the world. Elimination of *P. falciparum* malaria is the only strategy that can prevent the spread of resistance.

Although the evidence to support the effectiveness of MDA in the GMS is limited, the potential public health threat of spreading multidrug resistance warrants the use of extreme measures. The objective of MDA in this setting would be a rapid reduction in parasite burden and the

asymptomatic reservoir, which may be harbouring multidrug-resistant parasites, including artemisinin-resistant *P. falciparum* strains. In low-transmission settings, the objective would be rapid interruption of transmission; in moderate-to-high-transmission settings it would be rapid case reduction. The unit of intervention should be as small as operationally feasible, to maximize the impact in the target population.

4.2.3 Use of MDA to reduce morbidity and mortality during epidemics

Recommendation 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.

Malaria epidemics present as a sudden and unexpected increase of malaria cases and deaths (in the case of falciparum malaria) in time and space. They differ from the increase in transmission caused by seasonal fluctuations. Once the epidemic of malaria is confirmed, MDA can be considered as part of the immediate response to reduce morbidity and mortality while other interventions – notably case management, vector control and surveillance – are put in place. The role of MDA in the context of an epidemic would be rapid reduction in malaria morbidity and mortality, while concurrently alleviating burden on treatment centres. The unit of intervention would be the whole population within the region suffering from the epidemic, excluding groups mentioned in Section 4.1.3. The drug regimen can include PQ, to aid reduction of transmission.

4.2.4 Use of MDA, MSAT and FSAT to reduce morbidity and mortality during exceptional circumstances

Recommendation 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.

MDA should be considered as a temporary control measure in complex emergencies occurring in areas of moderate-to-high malaria transmission, when combating febrile diseases of a major proportion that share common signs and symptoms with malaria (e.g. an Ebola outbreak). Here, the aim of MDA is rapid reduction in malaria morbidity and mortality. MDA would have the benefit of reaching the whole population, including the most vulnerable groups, while alleviating pressure on overwhelmed health systems that are unable to serve all affected communities.

MSAT and FSAT are not recommended for use in the specific context of an Ebola outbreak, because testing adds cost and complexity and raises blood safety concerns without generating improved clinical outcomes for the population. In outbreaks of other pathogens, MSAT may have a role.

4.2.5 Use of MDA in areas with moderate or high transmission

Recommendation 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.

There is currently insufficient evidence to recommend the use of MDA, MSAT or FSAT in moderate- and high-transmission settings.1 Since there is currently only one ongoing study on this topic, it is recommended that a research consortium be developed, with the aim of collecting and overseeing evidence that can be used to inform future recommendations.

4.2.6 Use of MSAT or FSAT to reduce transmission

Recommendation 6

Using current diagnostic tests, MSAT and FSAT are not suitable as interventions to reduce malaria transmission.

MSAT is not recommended to reduce the asymptomatic reservoir of infection of either *P. falciparum* or *P. vivax* in islands using RDTs or microscopy as the screening method. Also, MSAT and FSAT using RDTs and microscopy are not recommended as tools to reduce malaria transmission, or for elimination of multidrug-resistant *P. falciparum* in the GMS.

FSAT should be distinguished from ACD, the detection of individuals who may have high risk of infection at community level. ACD is used for surveillance, and is generally conducted as part of epidemiological investigations, through house-to-house visits; it should be considered complementary to MDA.

1 See Table 1 in: Disease surveillance for malaria control. An operational manual. Geneva, World Health Organization (WHO). 2012 (http://whqlibdoc.who.int/publications/2012/9789241503341_eng.pdf, accessed 08 April 2015).

Annex 1 Meeting pre-reads

Publication	Country or continent	Study description
Canier et al., 2013 (41)	Cambodia	A mobile laboratory performing DNA extraction and real-time PCR enabled ACD of asymptomatic low-density parasite carriers in the field.
Canier et al., 2015 (42)	Cambodia	PCR was performed from 50, 200 and 1000 µL venous blood samples, and 5 µL DBS. Similar sensitivity was achieved from all venous blood samples, and was about 100-fold lower than the limit of detection from the DBS.
Cook et al., 2015 (40)	Zanzibar	Two rounds of MSAT (screening with *P. falciparum* RDT) in transmission hotspots did not reduce malaria incidence, which was attributed to low-density infections and presence of non-falciparum species.
Cupp et al., 2011 (28)	Africa and South America	Review detailing success of onchocerciasis control programmes using vector control or MDA with ivermectin at varying dosage intervals, which significantly reduced transmission in two African countries and interrupted transmission in seven regions in the Americas.
Emanuel et al., 2004 (43)	General	An overview of ethical considerations for multinational clinical research.
Hein et al., 2015 (44) (unpublished)	Viet Nam	Highly sensitive qPCR was applied to large blood volumes (>1 ml) to enable detection of low-density asymptomatic cases (which may include artemisinin-resistant strains), with the aim of TME.
Hoyer et al., 2012 (7)	Cambodia	Questionnaires and FSAT were used in cross-sectional surveys, with the aim of actively detecting asymptomatic carriers containing drug-resistant strains, and assessing the risk of parasite spread across borders. No artemisinin-resistant strains were found, and there was no cross-border movement of parasite carriers.
Hsiang et al., 2013 (10)	China	An ecological study evaluating relationship between MDA and malaria incidence in China during 1973–1983 (when the burden was high) and 2000–2009 (when the burden was low and focal).
Kaneko et al., 2014 (34)	Aneityum Island, Vanuatu	*P. vivax* was eliminated in 1996, but returned as an epidemic in 2002. Malariometric PCR and serology surveys of the entire population of Aneityum found that individuals born after the elimination programme began were more likely to be parasitaemic than older age groups; the latter also had higher levels of antibodies.
Kondrashin et al., 2014 (11)	Asia	A review of mass primaquine treatment for elimination of *P. vivax* in four countries. A 14 or 17 day treatment course was used in regions with up to 38.7% G6PD deficiency, with low frequency of severe AEs reported.
Kondrashin, 2008 (45)	DPR Korea	Report detailing post-elimination resurgence of *P. vivax* including parasite epidemiology, entomology and operational aspects, and successes of the MPPT campaign.
Larsen et al., 2015 (9)	Zambia	A randomized controlled trial that used three rounds of MTAT resulted in a reduction of malaria infection in children, and a reduction in outpatient case incidence, but did not reduce transmission to a low enough level to enable deployment of elimination strategies.

Publication	Country or continent	Study description
UCSF Global Health Sciences, 2014 (46)	Worldwide	Qualitative review that assessed key informant interviews and published literature, to document past and current MDA strategies and identify knowledge gaps.
MSF, 2015 (47)	Sierra Leone	Report detailing operational experiences of conducting MDA during the Ebola outbreak and the lessons learnt. Early results indicated high coverage and good compliance to drug regimens.
Oguttu et al., 2014 (48)	Uganda	Serological surveys using Ov16ELISA were employed to monitor progress of the onchocerciasis elimination programme. Statistical methods were re-examined, which resulted in the conclusion that a lower number of individuals need to be tested per survey.
Poirot et al., 2013 (4)	Asia, Africa, Europe, The Americas	A Cochrane systematic literature review evaluating quantitative impact of MDA studies from about the past 70 years.
Richards et al., 2011 (29)	Nigeria	Annual MDA with ivermectin and albendazole for 7–10 years significantly reduced burden of LF and enabled interruption of transmission in 5 out of 10 sentinel villages.
Sluydts et al., 2014 (49)	Cambodia	Malariometric surveys using PCR and SaTScan identified regions of elevated risk of infection for each plasmodial species. Risk was associated with staying in a plot hut and proximity to a river.
Smith et al., 2015 (50) (unpublished)	Sierra Leone	Preliminary report of MDA campaign during the Ebola outbreak, including planning strategies, operational challenges and coverage and adverse event data.
Song, 2015 (51) (unpublished)	Comoros and Cambodia	Report showing that MDA using AS-PIP and low-dose PQ reduced the parasite carriage rate but did not interrupt transmission in medium to low transmission regions in Cambodia and Comoros.
Stresman et al., 2015 (52) (unpublished)	Kenya	FSAT using PCR and RDT revealed that households with RDT-positive individuals were more likely to also have submicroscopic parasite carriers.
Tiono et al., 2013 (53)	Burkina Faso	Community-wide screen and treat of asymptomatic carriers using RDTs in 18 villages did not reduce clinical malaria incidence in the subsequent transmission season.
von Seidlein et al., 2003 (1)	Worldwide	Review article describing previous approaches to direct and indirect MDA, along with study successes and challenges.
von Seidlein et al., 2015 (54)	Worldwide	Review article discussing the spread of antimalarial drug resistance and containment strategies.

ACD, active case detection; AE, adverse event; AS-PIP, artemisinin-piperaquine; DBS, dried blood spots; DNA, deoxyribonucleic acid; DPR, Democratic People's Republic; G6PD, glucose-6-phosphate dehydrogenase; FSAT, focal screening and treatment; LF lymphatic filiariasis; MDA, mass drug administration; MPPT, mass primaquine prophylactic treatment; MSAT, mass screening and treatment; MSF, Médecins Sans Frontières; MTAT, mass test and treatment; PCR, polymerase chain reaction; qPCR, quantitative PCR; PQ, primaquine; RDT, rapid diagnostic test; TME, targeted malaria elimination

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