World Health Organization

15 September 2015

Malaria Policy Advisory Committee (MPAC) Draft Meeting Agenda
Dates: 16-18 September 2015. Location: Salle A, WHO HQ, Geneva

Wednesday, 16 September 2015

Time	Session	Purpose	Type
9.00 am 10:00 am	Session 1: Opening remarks, ADG/HTM *(Dr W. Mpanju-Shumbusho)* Welcome from Chair, MPAC *(K Marsh)* Report from the Director, GMP *(P Alonso)* Recommendations from MDA ERG/GRADE tables/Review of delivery cost data/ Background paper on MDA modelling/Presentation/Recommendations *(K Marsh)*	For information For decision	open
11.30 am	**coffee**		
12.00 pm	Session 2: Feedback on P. vivax technical brief and recommendation for G6PD testing before treatment/Presentation *(K Mendis)*	For discussion	open
1.00 pm	**lunch**		
2.00 pm	Session 3: Recommendations on when to scale back vector control/Presentation/ Information note *(N Chitnis/J Yukich/A Mnzava)*	For decision	open
3.30 pm	**coffee**		
4.00 pm 5.30 pm 6.00 pm	Session 4: Recommendations from ERG on malaria in pregnancy/Presentation/Recommendations *(R Leke)* Update on Policy setting process for WHO/GMP *(P Alonso)* WHO Study Group on Malaria Eradication *(P Alonso)*	For decision For information For information	open
6.30 pm	**End of day/ cocktail reception**		

Thursday, 17 September 2015

Time	Session	Purpose	Type
9.00 am	Session 5; Malaria Terminology *(R Steketee)*	For discussion	open

GLOBAL MALARIA PROGRAMME

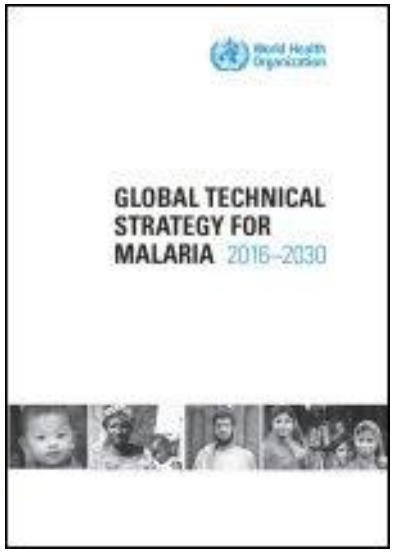
World Health Organization

Report from the Global Malaria Programme

Malaria Policy Advisory Committee
Geneva, Switzerland
16-18 September 2015

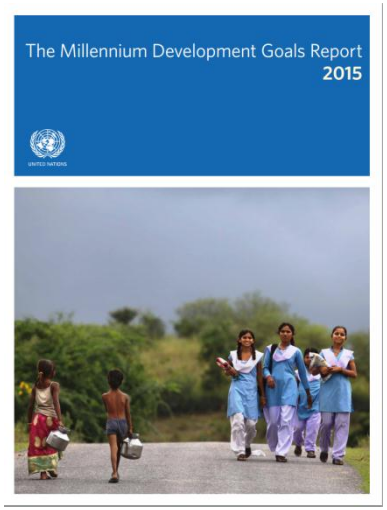
Pedro Alonso
Director, Global Malaria Programme
alonsop@who.int
On behalf of the global malaria team

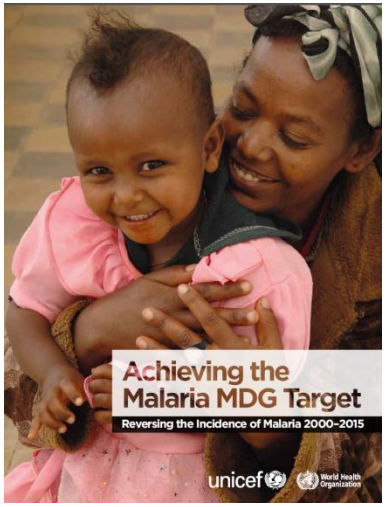
Global Technical Strategy for Malaria 2016-2030



- Endorsed by WHA in May 2015, joint GTS/AIM launch at 3rd Intl Conference on Financing for Development - Addis Ababa, July 2015
- Regional Plans in development
  - GMS strategy – May 2015 launch
  - AFRO – Sep 2015 consultation
  - SEARO – Oct 2015 draft
  - PAHO – Oct 2015 consultation
  - EMRO – Oct 2015 regional committee
  - WPRO – Dec 2015 consultation
  - EURO – Sep 2016

Millennium Development Goal Reporting





- UN secretary General report released July 6th with section on malaria
- Malaria MDG report written with UNICEF to be launched September 17th
  - Including new disease burden estimates
- Paper in Nature by MAP to be released the same day. The effect of malaria control on *Plasmodium falciparum* in Africa between 2000 and 2015.
  - With evidence base for change in parasite prevalence case incidence and that interventions are responsible for a substantial proportion of the change.

MDG Report Highlights

Table 1. MDG 6 and associated malaria target and indicators

Goal	6. Combat HIV/AIDS, malaria and other diseases
Target	6C. Have halted by 2015 and begun to reverse the incidence of malaria and other major diseases
Indicators	6.6 Incidence and death rates associated with malaria 6.7 Proportion of children under 5 sleeping under insecticide-treated mosquito nets 6.8 Proportion of children under 5 with fever who are treated with appropriate antimalarial drugs

Table 2. Malaria MDG indicators then and now

Indicators		2000	2015	% change
6.6	Incidence rate associated with malaria (per 1000 at risk) and Death rate associated with malaria (per (100 000 at risk)	146 47	91 19	–37% –60%
6.7	Proportion of children under 5 sleeping under insecticide-treated mosquito nets	2%	68%	>100%
6.8	Proportion of children under 5 with fever who are treated with appropriate antimalarial drugs*	0%	13%	>100%

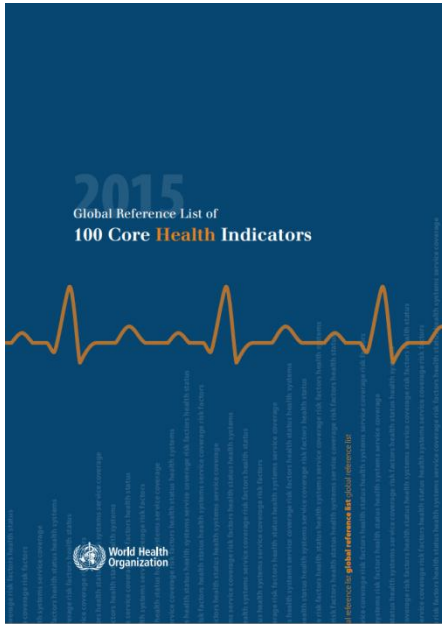
* Refers to artemisinin-based combination therapies

MDG Report – Other Statistics

	2000	2015
Estimated no. cases (millions)	262	214
Estimated no. deaths	839,000	438,000

Decline in malaria deaths rates in children <5 2000 - 2015	65%
Cases averted 2001 - 2015	1.2 billion
Deaths averted 2001 - 2015 (compared to if incidence and mortality rates 'of 2000 persisted 22001 to 2015)	6.2 million
Countries reporting zero cases in 2014	13
Countries reporting <10 cases in 2014	6

Global Reference List of 100 Core Health Indicators



- Aimed to be consistent with GTS core 14 indicators. Included:
  - Malaria mortality rate
  - Malaria parasite prevalence among children 6−59 months
  - Malaria incidence rate
  - IPTp for malaria during pregnancy
  - Use of insecticide treated nets (ITNs)
  - Treatment of confirmed malaria cases
  - Indoor residual spraying (IRS) coverage
  - Completeness of reporting by facilities
- Included in "additional indicators"
  - % of suspected malaria cases that had a diagnostic test
- Not included
  - Proportion of malaria cases detected by surveillance systems
  - % of cases investigated (programmes in elimination)
  - % of foci investigated (programmes in elimination)
  - Number of countries newly eliminated malaria since 2015
  - Number of countries that were malaria-free in 2015 in which malaria was re-established

Update on Roll Back Malaria Partnership

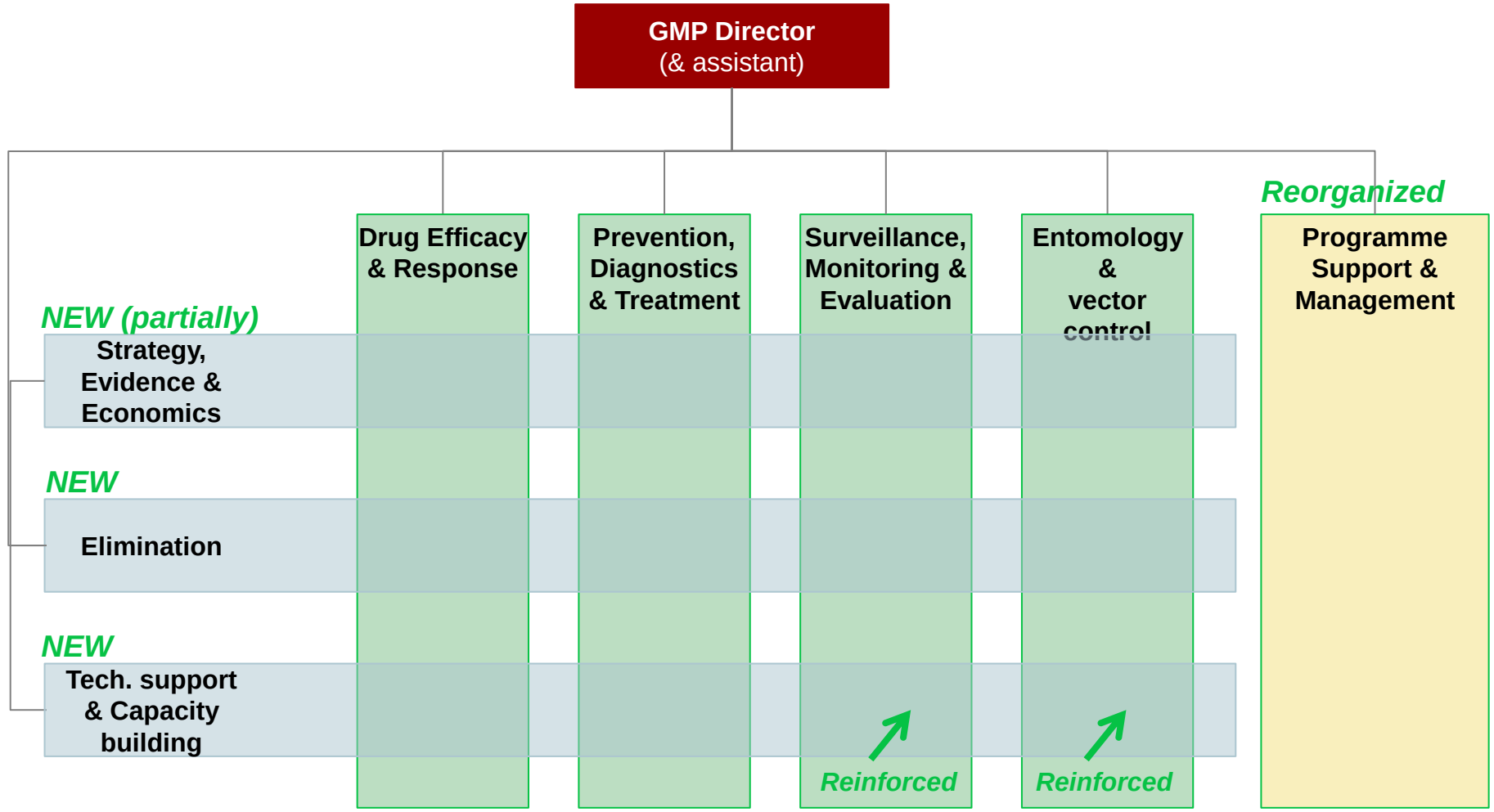
- A new partnership structure was approved by the RBM Board in May
- On 25 August, the chair of the RBM Board sent a letter to the DG on the Board decision to disestablish the RBM Secretariat based on a recommendation from the Finance and Performance Committee
- An Interim work plan for Sept – Dec 2015 and Secretariat Closure Timetable was prepared and approved by the FPC and the Executive Committee and sent to the Board on 9 Sept
- A Transition Oversight Committee, chaired by Zimbabwean Minister Parirenyatwa and Admiral Tim Ziemer has been formed to establish the new structure and develop plans for the transition
- WHO/GMP will work with the HWG and other partners to ensure that there is no gap in the technical support provided to countries

Since Last MPAC Meeting

- Guidelines for the treatment of malaria. 3rd edition (April 2015)
- Global Technical Strategy for Malaria 2016-2030 (June 2015)
- Indoor residual spraying: An operational manual for IRS for malaria transmission, control and elimination. Second edition (June 2015)
- Control and elimination of *Plasmodium vivax* malaria – A technical brief (July 2015)
- Eliminating malaria: Case study 10. Successful elimination and prevention of re-establishment of malaria in Tunisia (July 2015)

- Malaria Policy Advisory Committee to the WHO: conclusions and recommendations of March 2015 meeting - published August 2015

New WHO-GMP Matrix Structure



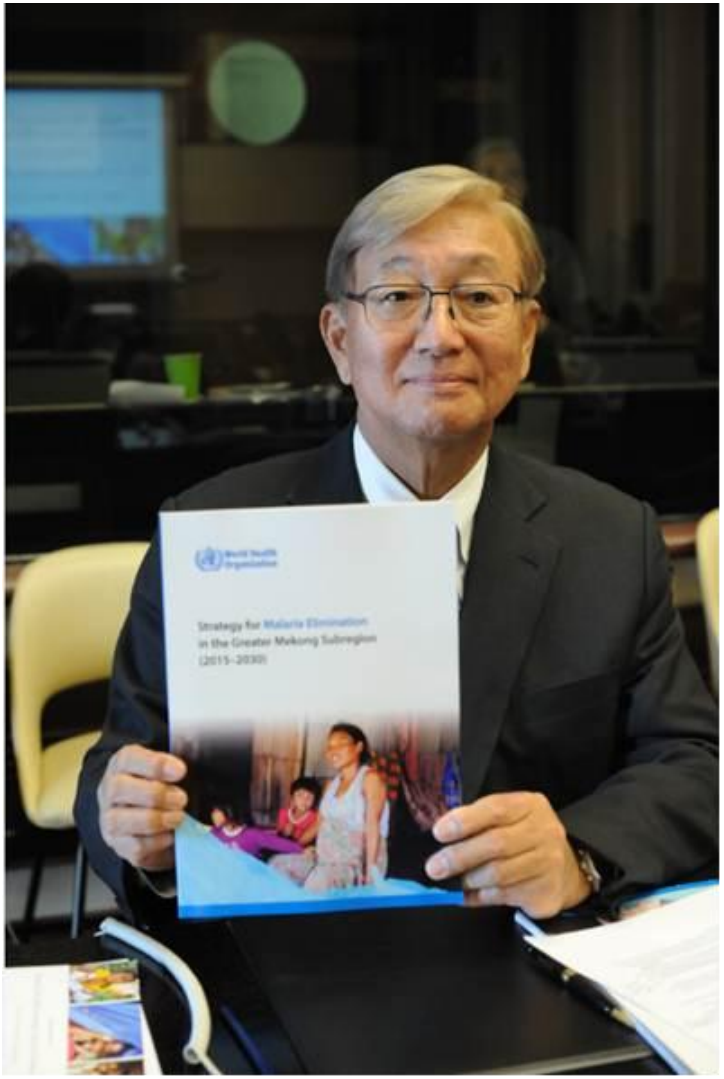
- Reinforcement of SM&E and Vector control teams
- Creation of 3 cross-unit teams to cover critical areas & enhance collaboration
- Strengthened support to department via Programme Support & Management

Drug Efficacy & Response (DER)

- Strategy for Malaria Elimination in the Greater Mekong Subregion (2015-2030) launched May 2015
- Status report on artemisinin and ACT resistance – September 2015

  Resulting in policy changes
  - Cambodia – DHA-PPQ to AS-MQ
  - Thailand – AS-MQ to DHA-PPQ
  - North-east India – AS-SP to AL
  - Sudan and Somalia – AS-SP to ?

  (deciding meetings to be held shortly)
- More details tomorrow in Session 6



Entomology & Vector Control (EVC)

- Strengthening the EVC team at HQ
- Published the revised version of the IRS manual – which now includes a checklist for environmental compliance
- Vector control technical support provided especially to countries which are about to eliminate malaria
- Work on the insecticide resistance global database proceeding well – with provision for online tools to generate maps
- Convening an ERG to define areas and conditions in which to deploy PBO nets following MPAC's advice to GMP

Entomology & Vector Control (EVC)

Innovation to Impact (I2I)

- EVC/GMP has contributed as a stakeholder to this important initiative
- Part of I2I, is a WHO reform in the following areas:
  - Stimulate development of more innovative products
  - Accelerate availability of vector control products
  - Improve quality of vector control products
  - Increased appropriate use of innovative vector control interventions
- Like medicines and diagnostics, evaluation of vector control products will be handled by PQ, while GMP and NTD will retain the normative piece
- Jointly with NTD, a grant proposal is being reviewed by BMGF and our two departments will be providing an update later during this meeting

Prevention, Diagnosis & Treatment (PDT)

- Malaria Treatment Guidelines (3rd Ed – March 2015)
- Collaboration with IVB for JTEG on RTS,S malaria vaccine
- ERG on MDA, MSAT and FSAT
- ERG on ISTp and safety of artemisinin derivatives in pregnancy
- WHO Drafting Committee on Malaria Terminology
- QA/QC for malaria diagnostics
  - Microscopy QA manual update
  - Malaria RDTs: R5 Product Evaluation and launch of R6
  - Preparation of international EQA scheme for NAA-based techniques
- Monitoring phasing out oral artemisinin-based monotherapies and procurement of QA ACTs and RDTs
- Preparations for PPC meeting on ivermectin for malaria
- RAcE 2015 implementation and policy development at country level

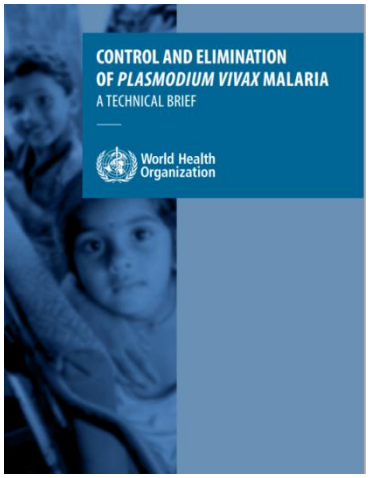
Surveillance, Monitoring & Evaluation (SUR)

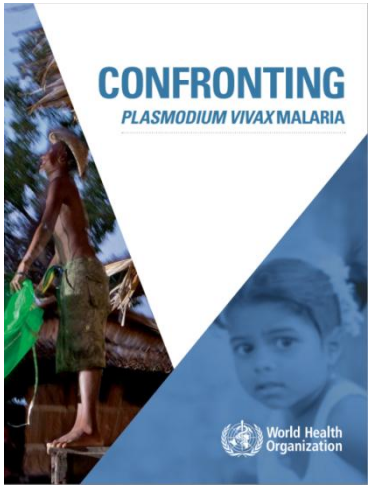
- Team Leader position under recruitment
- Data workshops (with support from Global Fund and jointly planned with SEE) for National Malaria Programmes in Africa to strengthen capacity of surveillance, monitoring and evaluation and conduct rapid impact studies
  - Helps disseminate surveillance guidance to countries and impart data analysis skills that will help contribute to the quality of data collected for the World Malaria Report
  - Critical need to invest in training and dissemination of guidance given that Surveillance is third pillar in GTS – we hope that data workshops will be an annual event in each region/IST

Elimination (ELI)

- Team Leader position under recruitment
- Elimination ERG
- Technical support to E8, GMS
- Second certification missions planned for: Argentina and Kyrgyzstan

Strategy, Evidence & Economics (SEE)





- Launch of *Plasmodium vivax* control and elimination: a technical brief, July 29th 2015 in New Delhi
  - With generous support from MMV and SEARO
- Confronting *Plasmodium vivax* malaria - an advocacy piece
- Editorial in Lancet infectious disease: *Plasmodium vivax*: a roadblock on the quest to eliminate malaria
- Workshop of 17 countries to present guidance and to include the *P. vivax* strategy in national malaria strategic plans

Technical Support & Capacity Building (SCB)

- Facilitated (3 workshops) the update of the Malaria Programme Review and Planning documents (Annual Planning Guide; Malaria Strategic Planning development manual; and the Malaria Programme Review Guide) for endemic countries. Next step is a validation workshop with all NMCP managers from the AFRO region to validate the tools (Proposed for November 2015)
- Mock TRP review of GF concept notes submission (7 countries). All successfully submitted their malaria concept note.
- Gap analysis workshop to update the resource gaps from 2016 – 2020. Forty two malaria endemic countries from AFRO /EMRO were in attendance
- Support mission to update national treatment guidelines based on the just published 3rd edition of the WHO guidelines (6 countries – AFRO/SEARO supported)
- National Malaria Strategic Plan review and update mission to Sierra Leone (post Ebola)
- Malaria Programme Review in Thailand

Technical Support & Capacity Building (SCB)

Continued to participation to support Global Fund activities

- Briefing and support to the Technical Review Committee (3 waves in the reporting period)
- Member of the GF Grant Approval Committee (3 meetings in the reporting period)
- GMP continues to chair the HTM cluster Joint Working Group on the GF

In addition:

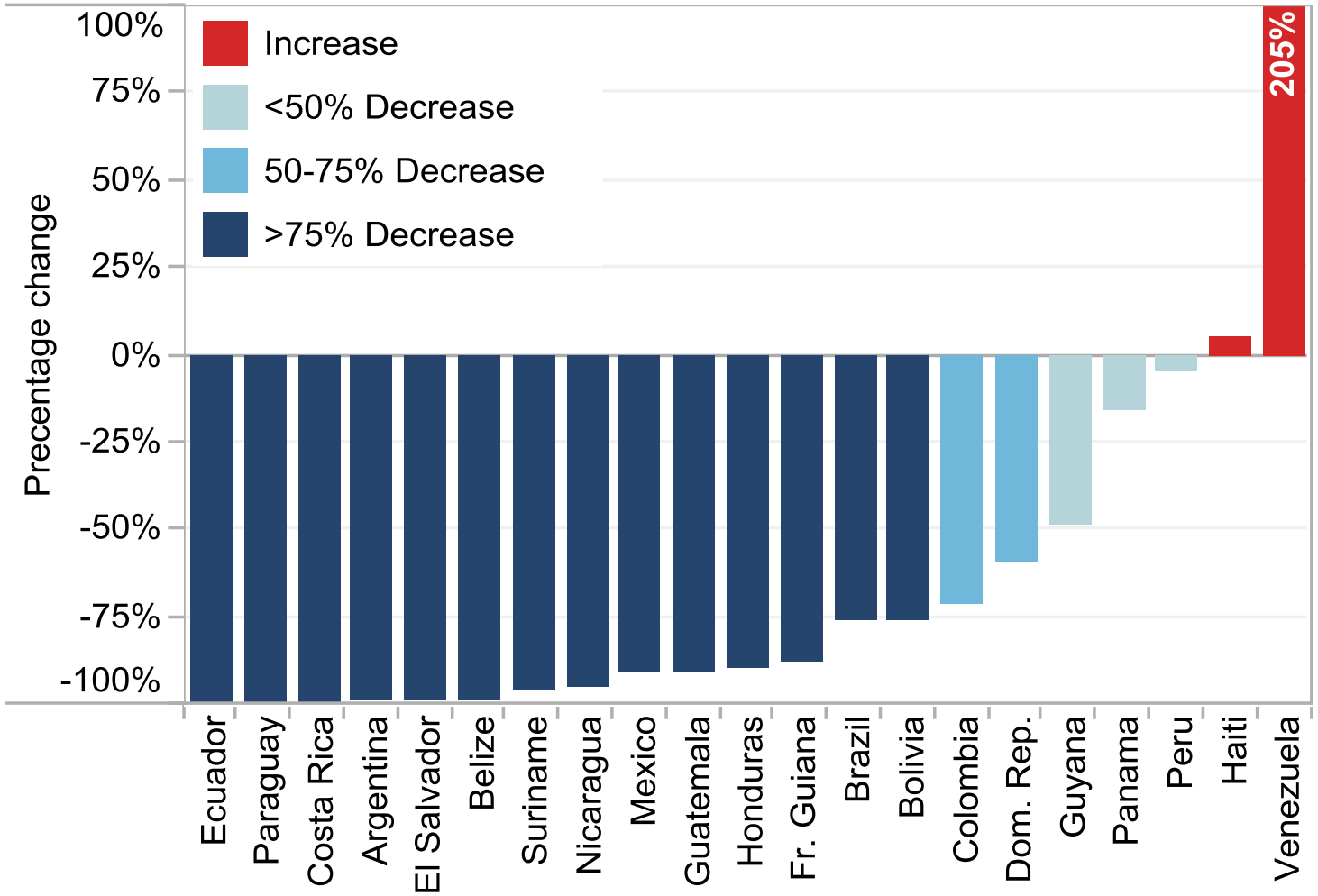
- Uganda – joint mission with IST/AFRO to assist in the epidemic response
- Sierra Leone – assisted with post Ebola National Strategic Plan update
- Djibouti – leading mission to plan for rainy season epidemic prevention
- Madagascar – leading a joint mission with AFRO to investigate upsurge in malaria cases and support GF concept note development

Anticipated WHO Guidance 2015/2016

- Guidance and policy briefings on malaria vaccine
- review of cardiotoxicity of antimalarials
- review efficacy and safety of pyronaridine+ artesunate
- review of QC methods for malaria RDTs for use at point of care
- review of *P. knowlesi* prevention and control
- preferred product characteristics of ivermectin use for malaria prevention
- Operational manual on diagnostics in low transmission
- Operational manual on mass drug administration
- Response plan to identified medicines safety concerns
- Entomological surveillance manual
- Vector control country mapping tool
- Framework for insecticide resistance monitoring and management
- LLIN durability to guide procurement decisions
- Elimination field manual
- Update on WHO terminology for malaria
- Framework for SME of GTS & AIM 2016-2030 (WHO and partners)
- Up to date field-level guidance handbook on SM&E implementation

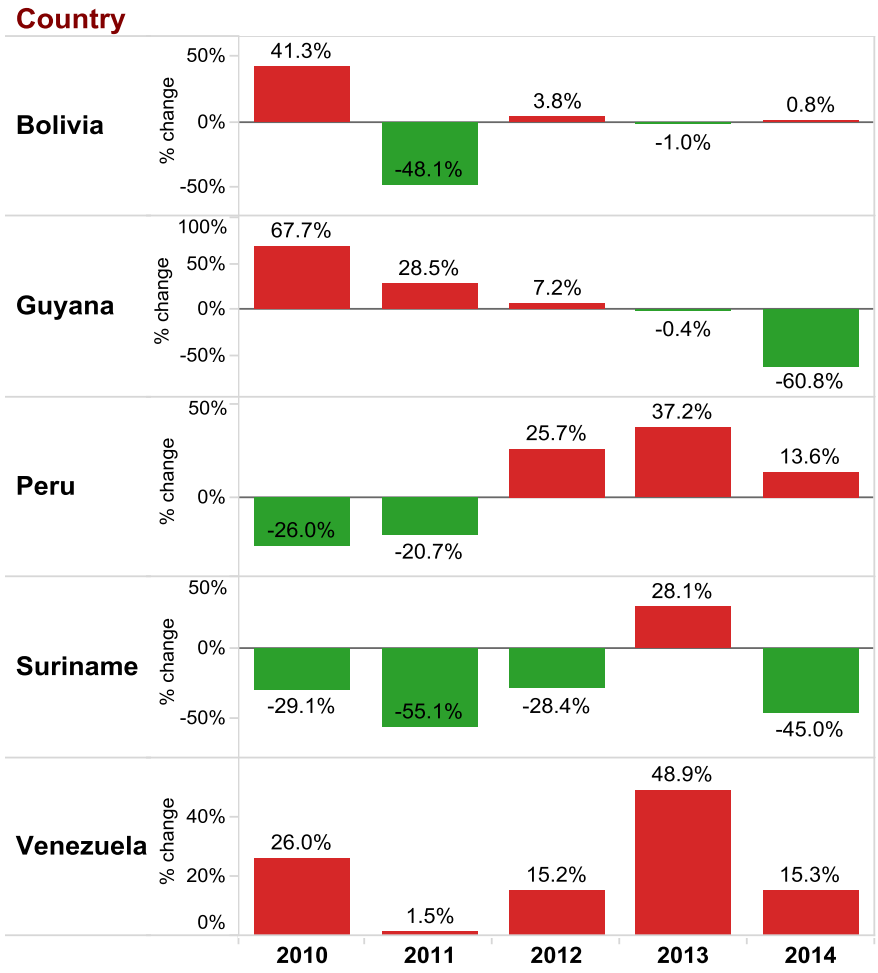
Regional Updates

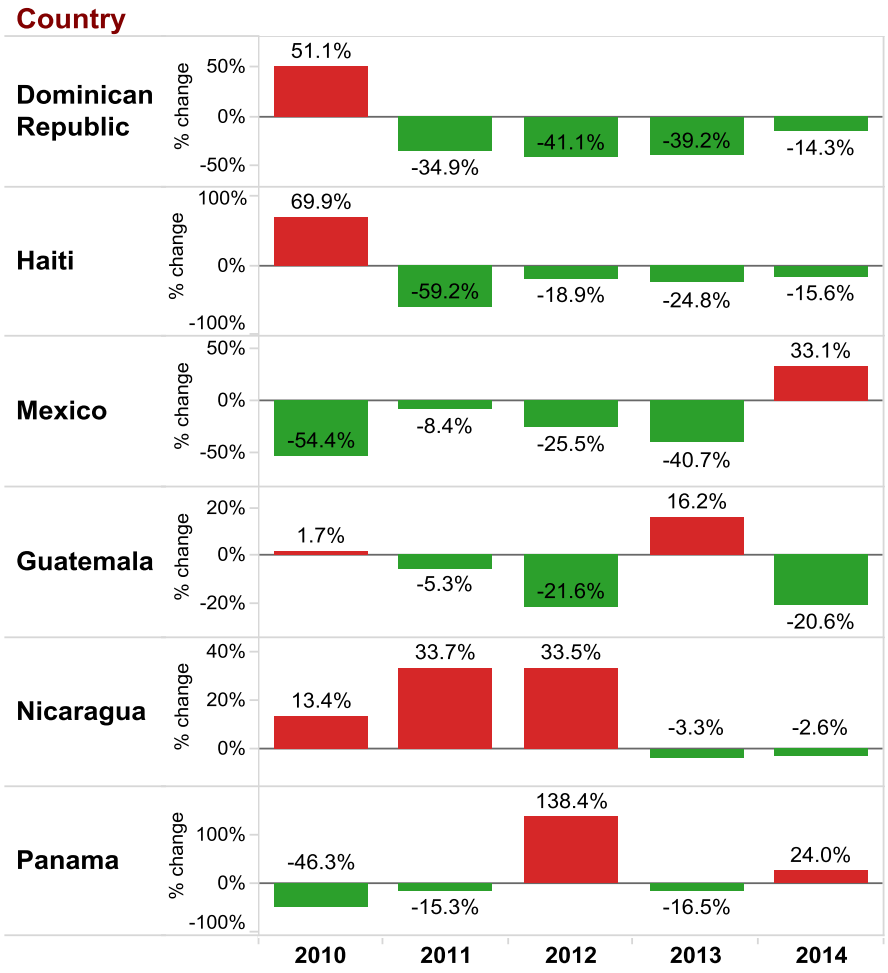
Decrease in Malaria Morbidity by Countries of the Americas, 2000–2014



** Fr. Guiana - French Guiana, ** Dom. Rep. - Dominican Republic*

Percentage Change in Malaria Morbidity from the Previous Year, 2010-2014

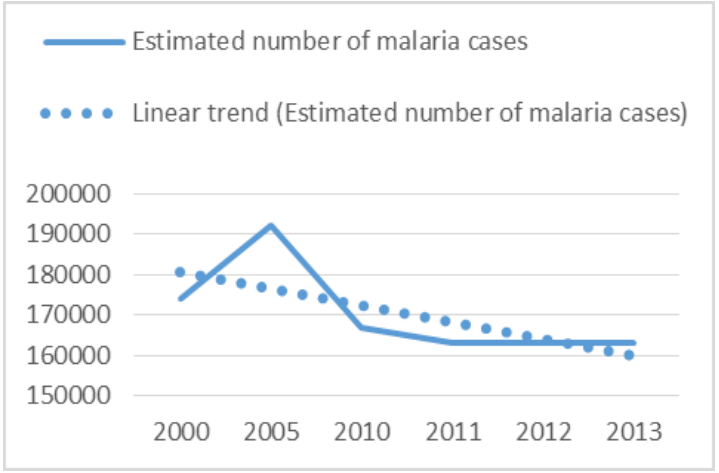


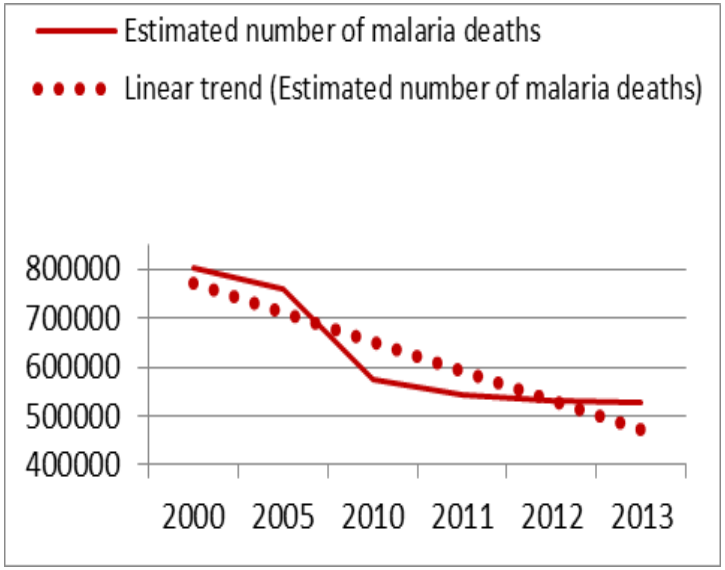


High Burden Countries & Great Progress

- 18 countries in Africa account for 90% of infections in sub-Sahara Africa
- 2 countries account for 40% (Nigeria 29% and DR Congo 11%)
- Therefore, achievement of 40% reduction needs impact in high burden countries

Malaria incidence decreased by 34% and mortality declined by 54% in the African Region between 2000 and 2013





Source: WHO World Malaria Report 2014

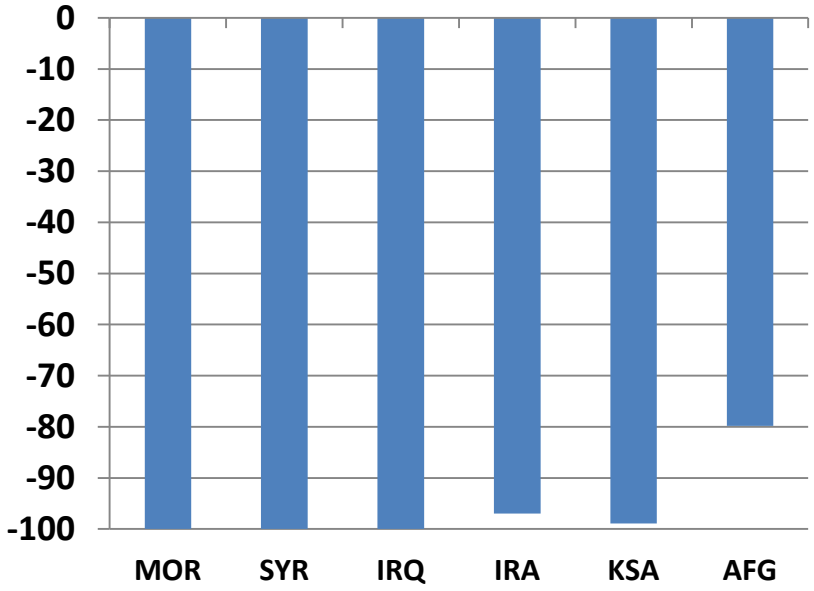
Challenges

- Gaps in interventions coverage and utilization
  - Only 29% of HHs had enough ITNs for all HH members in 2013
  - A third of HHs did not own even a single ITN in 2013
- Lack of robust, predictable and sustained international and domestic funding
- Inadequate HR capacity in AFRO (countries, IST, RO) to support implementation of the Global Technical Strategy for Malaria and the Africa Malaria Strategy
- Inadequate performance of malaria programmes & health systems
- Rising insecticide and antimalarial resistance & absence of novel tools/technologies

Achievements, Challenges in EMR

Achievement of MDG related to malaria in EMR countries

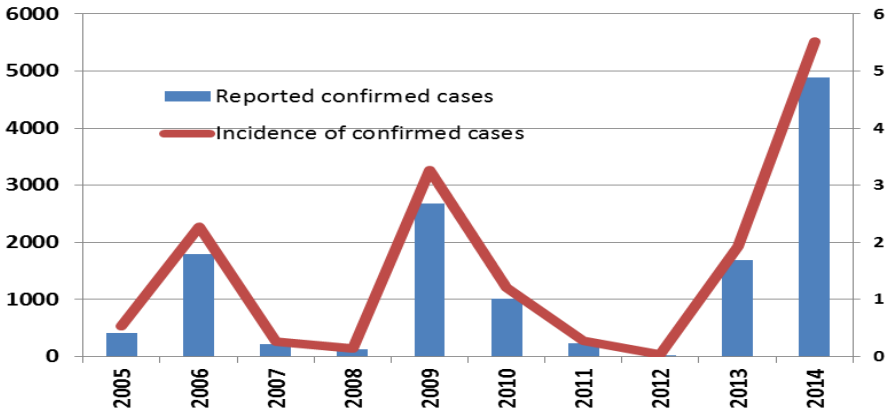
% reduction of reported confirmed malaria cases 2000-2014



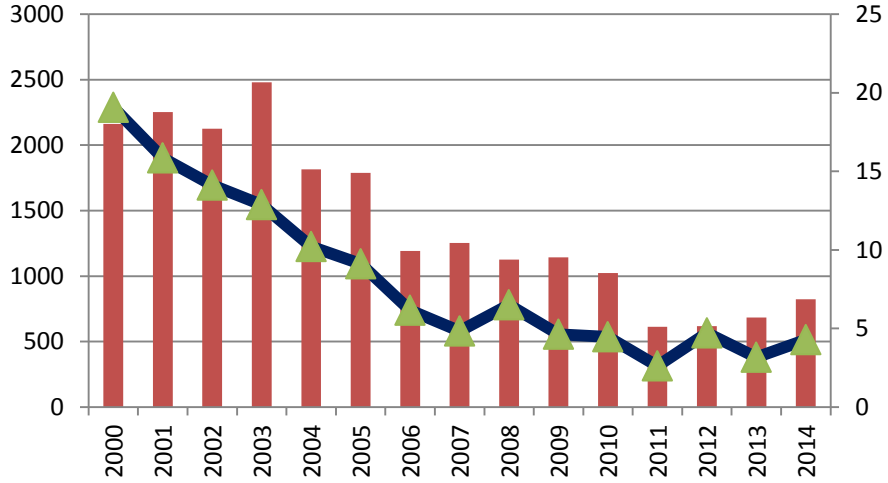
2014 : Local cases in Iran 370

Local cases in KSA 51

Epidemic in Djibouti



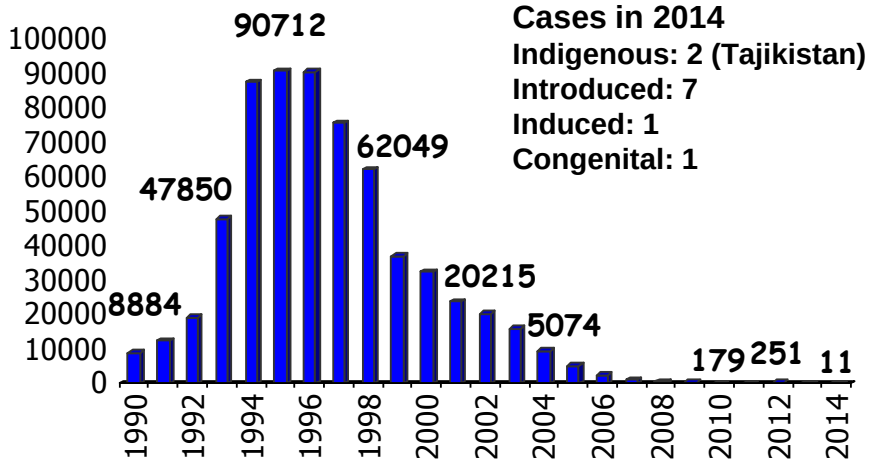
Mortality in Sudan



Elimination of Malaria in Europe

Cases in 2015

- Tajikistan: 1 case, registered in January, relapse
- Georgia: 1 induced case
- Greece: 1 case, Trikala, Farkadona municipality, Thessaly region, introduced



Prevention of reintroduction:

- Azerbaijan; Georgia; Uzbekistan
- Certified: Turkmenistan (2010); Armenia (2011); Kazakhstan (2012); Kyrgyzstan (2015)?

Elimination:

- Tajikistan; Turkey

Risk of reintroduction

- -Tajikistan: Border with Afghanistan
- -Turkey: Influx of refugees

Update on Malaria Control and Elimination in SEARO

Country	Target year for elimination and remarks
1. Bangladesh	2020; not feasible; NSP will be revised
2. Bhutan	2018; feasible; cross-border collaboration with India being strengthened; 11 indigenous case in 2014
3. DPRK	2020; 11,000+ cases reported in 2014; intensive operations needed to reach elimination goal by 2020
4. India	over 90% of districts with API less then 1/1,000; pre-elimination phase in the whole country by 2017; elimination by 2030; elimination plan to be launched in Feb 2016
5. Indonesia	2030; subnational elimination on track; 230 districts already declared malaria free
6. Myanmar	2030; significant progress; NSP being updated
7. Nepal	2026; feasible; it could be achieved earlier than 2026
8. Sri Lanka	zero indigenous case since Oct 2012; certification being planned in 2016
9. Timor Leste	significant progress; elimination goal agreed but target year not yet decided; feasibility assessment to be done before end of 2015
10. Thailand	2024; feasible; MPR done recently; NSP being updated

Update from the Western Pacific Region

- Over 700 mio people are at risk for malaria in 10 countries. Deaths were reduced by 93% since 2000; all countries are projected to decrease case incidence by >75% between 2000 and 2015. Cases due to *P. knowlesi* are increasing, esp. in Malaysia.
- All endemic countries have malaria elimination goals in their updated National Strategic Plans. By 2020, 3 countries are expected to achieve elimination: Republic of Korea, Malaysia, China (50 indigenous cases).
- Malaria has resurged in Lao PDR since 2011. Due to most countries having moved to middle income category, external funding has been severely cut esp in the high transmission countries in the Pacific such as PNG, with high risk of losing the huge gains made.
- Recent increase in Cambodia, deteriorating multi-drug resistance in the Mekong Region
- Major challenges are: Covering all populations at risk for malaria, esp mobile/migrant populations; appropriately dealing with vivax malaria; adequate human resources and funds to accelerate malaria elimination.

Thank you to MPAC Members

- Salim Abdulla
- Elfatih Malik
- Patricia Graves
- Allan Schapira

Welcome to new MPAC Members - 2016

- Ahmed Adeel
- Tom Burkot
- Gabriel Carrasquilla
- Azra Ghani
- Gao Qi

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
WHO Headquarters, Geneva 20–22 April 2015

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.

WHO/HTM/GMP/MPAC/2015.9

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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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.

Malaria Policy Advisory Committee Meeting

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

Review of delivery cost data on mass drug administration for malaria

August 2015

A review of published and unpublished experiences of implementing mass drug administration (MDA) for malaria was conducted, to collect information on implementation cost and to estimate the unit delivery cost. The methodology is described in Annex 1. The review focused on the costs of delivering MDA; those costs include personnel, transportation, social mobilization, supplies, and so on, but exclude the cost of antimalarial drugs.

Cost data were collected for three experiences of using MDA for malaria, all using door-to-door MDA delivery. Two were implemented in island settings (Comoros and Vanuatu) and one in an emergency scenario (Sierra Leone). The experience in Vanuatu is described in a peer-reviewed publication (1), which also provides some delivery cost information. The other two experiences are described in reports (2-4), with cost data provided through personal communications by the implementing agencies to GMP in June to July 2015. Cost estimates are presented here in 2015 United States (US) dollars.

Cost data were available on:

- drugs, personnel, transportation, supplies, equipment and utilities in Comoros;
- drugs, local transportation and travel allowances, medical supplies and bednets in Vanuatu; and
- drugs, other medical supplies, non-medical supplies, personnel, transport, utilities and other recurrent costs in Sierra Leone.

Targeted populations in these experiences ranged between about 720 people in Vanuatu, 680 000 in Comoros and 3.05 million in Sierra Leone.

The antimalarial drug cost, including international shipment cost, was estimated at $ 2.33 per person-round using Artequick and primaquine in Comoros; at $ 1.23 for all nine weekly combinations of primaquine, chloroquine and sulfadoxine-pyrimethamine (SP) ($0.14 per administration) in Vanuatu; and at $ 1.00 using artesunate-amodiaquine (ASAQ) in Sierra Leone.

The delivery cost per covered person-round varied greatly across the three experiences: $ 11.05 in Comoros, $ 4.73 for all nine weekly administrations ($ 0.53 per administration) in Vanuatu and $ 0.36 in Sierra Leone. Figs. 1, 2 and 3 show the cost breakdown for each programme.

One would expect a lower unit cost with a greater number of people targeted because of economies of scale. Evidence on the delivery cost of MDA for neglected tropical diseases (NTDs) suggests a delivery unit cost lower than US$ 0.50 in most countries for interventions covering 100 000 people or more (5). A mean cost of less than $ 0.50 per person treated, excluding drug cost, was also reported on MDA for lymphatic filariasis and onchocerciasis in sub-Saharan Africa (6).

WHO/HTM/GMP/MPAC/2015.10

In Comoros, the high unit delivery cost relative to the programme scale might reflect personnel cost (32%), which included both international and local resources (per diems for international officials, expert consultancy cost and local training per diems). There was not enough information to dissociate international versus local personnel costs. It is, however, likely that excluding international related costs would lower the unit delivery cost. Similarly, transportation cost (20%) included both internationally and local transport costs (Figure 1). By removing the international transport component, the unit cost per person-round in Comoros would drop down below $ 9.50. Finally, in Comoros, supply costs (29%) (Figure 1), included the costs of social mobilisation and promotion and office supplies. It is likely that the costs of social mobilization and promotion represented most of those supply costs.

In Vanuatu, the delivery cost per person covered by 9 weeks of MDA was estimated at $ 4.73, equivalent to $ 0.53 per weekly administration. It included the costs of transportation and travel allowance (85%) and equipment and supplies costs (15%) (Fig. 2). There was not enough information available to estimate the cost of local versus international transportation and the share of other resource costs, such as personnel (Fig. 2).

In Sierra Leone, MDA was implemented in eight districts during the Ebola outbreak. The average delivery cost per person-round was estimated at $ 0.36, ranging between $ 0.29 and $ 0.39 across districts. In the two districts supported by Médecins Sans Frontières (MSF) Spain, the average delivery cost per person-round was estimated at $ 0.39. In the six districts supported by the national malaria control programme (NMCP) and the United Nations Children's Fund (UNICEF), unit costs ranged from $ 0.29 to $ 0.38. Differences in unit delivery cost across districts are mainly driven by the targeted population size (i.e. generally lower delivery unit cost with larger targeted population size) and the share of central level coordination cost allocated to each district by targeted population size (i.e. higher coordination cost share allocated to districts with larger targeted population size). In the two districts supported by MSF, personnel cost accounted for 50% of the unit delivery cost, central level coordination for 21%, local transport for 15%, utilities for 6% and supplies and equipment for 4% each (Fig. 3).

There are several limitations to the delivery cost estimates for MDA malaria presented here. First, we identified cost information for three MDA experiences only, and found huge cost variations across these experiences, which seriously limit the potential for comparison or generalization across settings. Second, cost information, where available, was often lacking in. Cost data were provided as totals for large categories of resources, such as personnel, transport, supplies and so on. It was therefore generally challenging, or not possible, to distinguish between the costs of:

- start-up or planning phase versus roll-out phase;
- local and international resources;
- central versus district level resources; and
- recurrent versus capital or fixed costs.

Furthermore, there were uncertainties about the cost of antimalarial drugs, which would affect the estimation of MDA unit delivery cost. Third, the limited data available related to financial costs only. No information was available for estimating economic costs that would capture the value of all resources, irrespective of whether these involved an additional direct cost. For example, where available, personnel cost data included the financial cost of per diems but excluded salary cost data, which would be necessary for placing a value on the time spent by personnel on MDA, and to inform policy makers on the true amount of resources required. Similarly, information on the cost of using vehicles or storage facilities that existed prior the MDA implementation was often lacking. Fourth, there was no information on the cost of research that may have been conducted during the implementation (e.g. to assess compliance rates) so it was not possible to exclude those costs from the MDA unit delivery cost. Further

research on the cost of implementing MDA for malaria is required, particularly research using ingredient-based costing approaches, where possible.

Figure 1: MDA delivery cost breakdown in Comoros

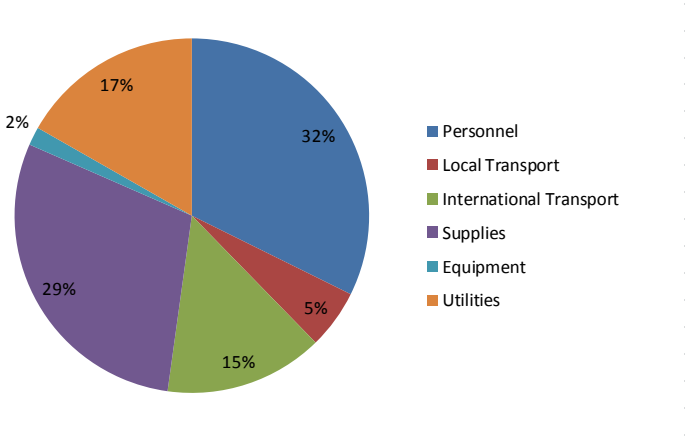

Figure 2: MDA delivery cost breakdown in Vanuatu

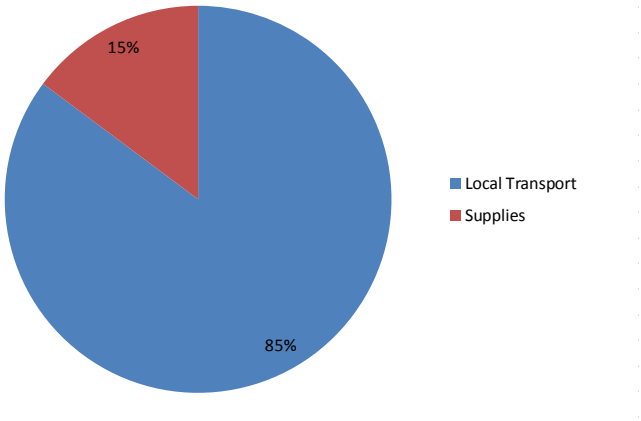

Figure 3: MDA delivery cost breakdown in Sierra Leone (Western areas)

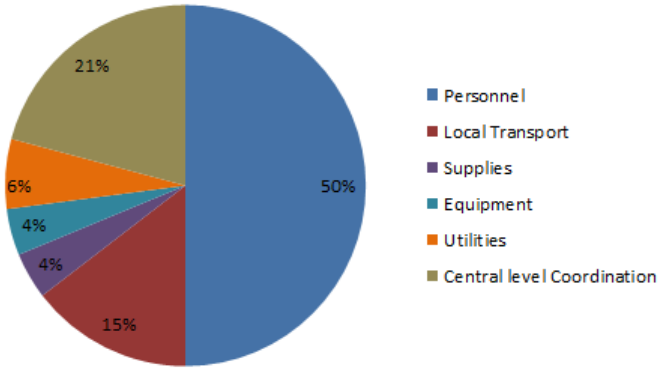

Table 1 Available evidence on the cost of MDA for malaria (costs in 2015 US$)

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

ASAQ, artesunate-amodiaquine; CQ, choloroquine; n/a, data not available; PQ, primaquine; SP, sulfadoxine-pyrimethamine

[a] Obtained by deducting drug cost to the total cost, and by dividing by number of people targeted or covered

[b] Three locations (Moheli, Anjouan and Grand Comoro), of which two (Anjouan and Grand Comoro) had two rounds and one had three rounds. We used two rounds for the cost calculations because 95% of the population targeted received two rounds (2).

[c] This is an average of the coverage achieved among the 95% population targeted at round one of two locations (2).

[d] Cost of treatment in Comoros using Artequick was estimated at $ 2.33, based on data provided by the implementer.

[e] Unit delivery cost was estimated at $ 9.45 per person-round when excluding international personnel transportation costs

[f] Kaneko et al report a total cost per person at $ 9.00, including $ 5.60 for bednets, $ 0.70 for antimalarials, $ 0.40 for materials and diagnosis and $ 2.30 for transportation and personnel (1). Published cost figures were assumed to be in $ 1991 and were converted to $ 2015 equivalent. We estimated the total cost per person at $ 5.95, with a delivery cost (excluding drugs) of $ 4.73 per person. It was assumed that the 9 weekly administrations corresponded roughly to one round.

[g] Sum of district-level data on targeted populations (4).

[h] Average of district level coverage rates (4), except for western areas, for which coverage rates reported by MSF Spain were used (3).

[i] Cost data reported by MSF Spain combined with cost data reported by NMCP (personal communications, July 2015) were used. It was assumed that the drug cost reported by MSF Spain represented the drug cost for the two districts (western area) supported by MSF Spain, and that the drug cost reported by the NMCP represented the drug cost for the six districts supported by NMCP/UNICEF (i.e. that there was no overlap between the organisations' drug expenditures). It was also assumed that the cost of central coordination reported by the NMCP was shared across all eight districts, by apportioning the total cost of central coordination to each district using the share of the total number of people targeted in each district.

[j] Weighted average cost per person covered per round across all eight districts.

Annex 1

A Pubmed search was conducted in July 2015 using a set of key terms, with publications restricted to those written in English or French, and published between 01 January 1950 and 01 July 2015. A total of 161 references were retrieved. The key terms used were:

(mass drug administration malaria OR chemoprevention malaria OR intermittent preventive treatment malaria OR mass screening and treatment malaria OR focal screening and treatment malaria) AND (economics OR costing OR costs OR financial OR economic OR funding OR funds OR cost OR resources OR price OR prices).

Whilst the initial search strategy aimed to identify cost information from MDA as well as other interventions like chemoprevention, intermittent preventive treatment and focal screening and treatment for malaria, cost information from MDA programmes only were reviewed for the purpose of this background document.

Key informants working in organisations involved in implementing MDA for malaria were contacted in June 2015; those contacted are listed in Table A1.

Table A1 List of key informants contacted

Country of implementation	Organisation or person contacted
Cambodia, Comoros	MOH/Guangzhou University of Chinese Medicine
Republic of Tanzania (Zanzibar)	IHI, S. Abdullah
Sierra Leone	MSF and NMCP/UNICEF
Vanuatu	A. Kaneko

IHI, Ifakara Health Institute; MOH, ministry of Health; MSF, Médecins Sans Frontières; NMCP, national malaria control programme; UNICEF, United Nations Children's Fund

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Malaria Policy Advisory Committee Meeting
16–18 September 2015, Geneva, Switzerland
Background document for Session 1

Consensus modelling evidence to support the design of mass drug administration programmes

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Executive summary

- In 2015 the MPAC will consider the evidence for the use of MDA in low transmission settings
- To support this the MMC conducted a model comparison exercise to identify the most important determinants of MDA effectiveness
- A variety of MDA operational considerations were included and their effect in different transmission settings analysed
- The outputs from four models were compared and consensus answers were reached on the following results:
    1. MDA with long-lasting ACTs is predicted to reduce transmission over a much longer timescale than the persistence of the prophylactic effect alone. Percentage reduction in transmission will be higher and last longer at lower baseline transmission levels.
    2. Treating a large proportion of the population in a single year in at least one round is a key determinant of MDA effectiveness whether it is achieved through high coverage in a single round, or reaching new individuals by implementing additional rounds.
    3. MDA will be more effective if conducted in the low transmission season and over longer time periods however the effect of the timing is small relative to other operational factors, if high coverage is achieved
    4. Varying the time interval between rounds from 4 to 6 weeks and the addition of primaquine to MDA with ACTs has little additional impact on transmission, even in the context of artemisinin resistance
- There is a high degree of consensus among the models on the relative influence of the operational factors analysed
- Differences in the predicted impact size arise due to the different assumptions made about malaria transmission in each model which represent realistic uncertainties in our understanding of this process

Introduction

In September 2015 the Malaria Policy Advisory Committee (MPAC) will review the evidence for the effectiveness of Mass Drug Administration (MDA) in low transmission settings. This will include the use of MDA for long term transmission suppression and elimination purposes as well as its use for epidemic containment and emergency response.

To complement the field trial evidence assembled separately by the Evidence Review Group (ERG) in April 2015, four groups from the Malaria Modelling Consortium (MMC) have conducted the following analysis to identify the consensus results among four established malaria transmission models on the effectiveness of MDA under different operational configurations and in different transmission settings. The analysis was limited to specific requests to address the key issues arising from the ERG and does not necessarily cover all questions on optimal and strategic deployment of MDA which further modelling work could help inform.

Given the large number of different possible combinations between MDA programme options and transmission setting characteristics (Table 1) measuring the effect of MDA effectiveness in each of these combinations using standardised field trials is infeasible and impractical. Instead malaria transmission models can predict what changes we might expect to happen given the field trial results we have already observed. Effectiveness or impact, for the purpose of this analysis is defined as the percentage reduction in annual average *Plasmodium falciparum* parasite rate as measured by PCR ($Pf\text{PR}_{\text{PCR}}$) in individuals of all ages three years after the last year of a given MDA programme.

Mathematical models are a useful way of evaluating the knowledge accumulated from existing MDA field trials. The models on display in this report have all been fitted to the MDA trials data as well as epidemiological data accumulated from malaria studies. While there is no way to guarantee that the mechanisms in these models are correct, or that the differences in the models do not explain the differences in their outcomes, the results of the models are consistent with most of the published data about malaria epidemiology and transmission. Most importantly though, the models may disagree in small ways, but they agree overall about the patterns and likely outcomes of MDA to such an extent that they can be used to support some robust policy recommendations on the use of MDA.

Previous modelling work from different modelling groups has identified some common themes on which factors are most likely to be important for optimising the use of MDA for malaria elimination(1-6). While interpreting these general trends from independent work is valuable, each of these analyses was performed in different epidemiological settings with different assumptions about how MDA is performed and the effect that it has. This hinders any formal comparison of the results derived from the models as we cannot be sure if differences arose due to the different input values of the models, or due to the different assumptions about malaria transmission made by each model. While it is important to standardise inputs and outputs for a formal model comparison, differences in model formulation and validation (see Appendix) represent important uncertainties in our understanding of malaria transmission that should be preserved in any output.

In this model comparison exercise we standardise the inputs and outputs of each of the models to derive directly comparable MDA effectiveness results for the first time. This has the advantage of being able to produce consensus quantitative estimates of effectiveness under different scenarios, whilst incorporating the uncertainty in modelling the malaria transmission process. The aims of this quantitative model comparison are as follows:

Aims

1. Via a limited number of simulation scenarios of operationally feasible MDA, we aim to estimate the impact of MDA on prevalence in low transmission settings
2. Additionally, this report aims to investigate model consensus on optimal strategies (among the operationally feasible strategies examined) to implement MDA in different low transmission settings

Methods

These aims are investigated through a series of simulations that analyse the changes in effectiveness of MDA from a baseline scenario in response to changing MDA operational characteristics. The baseline scenario was developed in collaboration with MDA field trial partners to most closely represent the transmission settings and operational constraints of MDA that are reported by the ERG. Parameter values for the baseline scenario are shown in Table 1. The output effectiveness metric for all analyses was the percentage reduction in annual mean $Pf\text{PR}_{\text{PCR}}$ in the 3rd year after the final year in which MDA is implemented (see example output in Figure 1).

Table 1 Parameters for the baseline scenario. * Effective coverage is defined as: the percentage of the population that take the full course of drug which clears all parasites (access to intervention x adherence x drug efficacy). The denominator corresponds to the entire population and those not covered includes those ineligible *e.g.* pregnant women and individuals under 6 months of age

Parameter	Value
Programmatic considerations	
Number of MDA rounds per year	2 rounds
Effective coverage*	70%
Coverage correlation between rounds	1 (same people are treated in each round)
Interval between rounds	5 weeks
Duration of MDA programme	2 years
Time of year MDA begins	Optimal (as defined by each group) in a Zambia-like seasonality
Other interventions	ITNs at 80% effective coverage and access to passive treatment with ACTs at 60%
MDA drug choice	Long-lasting ACT with properties similar to DHA-piperaquine
Addition of low-dose primaquine (0.25mg/kg) to MDA drug	No
Transmission setting characteristics	
Baseline transmission intensity	5% PfPR2-10 as measured by microscopy
Importation of malaria cases	None
Population size	10,000 people
Arteminisin resistance	0%
Seasonality profile	Zambia-based single season profile

Primaquine analysis

To investigate the additional impact of adding low dose (0.25mg/kg) primaquine to MDA with long lasting ACTs, two simulations of the baseline scenario were run, one with primaquine and one without. The MORU modelling group also implemented a corresponding analysis, but in the presence of artemisinin resistance.

Key operational variables

Among the fixed variables in the baseline scenario (Table 1) there is a subset of key operational variables that are of primary interest as they can be adjusted in an MDA program. These variables were investigated in a multivariate analysis which simulated the baseline conditions (Table 1) with every combination of the following core variable parameters (giving 2 x 4 x 3 x 2 = 48 different scenarios):

1. Number of rounds per year (2 or 3)
2. Effective coverage of each round (30%, 50%, 70% or 90%)
3. Weeks between each round of MDA (4, 5 or 6)
4. Duration of MDA programme (1 or 2 years)

This allowed us to observe the effect of changing any one of these variables, either in isolation, or in combination to test for potential interactions between the variables.

Predicted effect in different contexts

In this analysis we also tested how the effectiveness of a typical MDA programme might vary in different transmission settings. This involved re-running the baseline scenario (Table 1) but changing each for the following variables in isolation (one variable at a time):

1. Seasonal timing of MDA rounds (in settings with 1 or with 2 rainy seasons)
2. Starting *Pf*PR in 2-10 year olds as measured by microscopy (0-10%)
3. Imported infections per 10,000 people per year (0, 0.4, 1.6)
4. Population size (1000, 3000, 10000 people)

Summary of model differences

The key elements that differ between the models that are likely to impact the outcomes are summarised in the Appendix. The most important structural difference is between the three stochastic model systems (OpenMalaria, EMOD DTK and Imperial) and the MAEMOD deterministic model. Further differences between all the models include the way they represent the relationship between EIR and prevalence, human immunity, super-infection, and clonality of infections. Furthermore the data used to fit and validate the models differ with OpenMalaria, EMOD DTK and Imperial primarily using data from sub-Saharan Africa and MAEMOD using data from the Greater Mekong Sub-region. Only a full harmonisation exercise would dissect the precise cause of differing magnitudes of predictions in MDA impact given by each of the models and this was not carried out due to limited time for the exercise. In this analysis we focus on the consensus results and the relative impact of MDA with different operational characteristics.

Results

Example model output

Simulations of the baseline MDA scenario and its impact on all-age $PfPR_{PCR}$ from each of the four models is shown over time in Figure 1. Immediately following MDA there is a dramatic drop in prevalence due to successful cure of infection and the prophylactic effect of ACTs with a long half life. However in the absence of elimination, the prevalence of infection is predicted to return to pre-intervention levels (albeit at different rates depending on the model), a feature termed resilience in malaria transmission models. The reason for this is that the key factors which determine local transmission intensity and therefore prevalence of infection are the local density of mosquitoes, their rate of biting humans, and the rate at which infected humans clear parasitaemia. Once inhibitory blood drug levels decline in those participating in the MDA, none of these factors have been changed permanently, and thus transmission will re-establish at pre-MDA levels. Without some other change, such as improved vector control, the effects of MDA are likely to be transient.

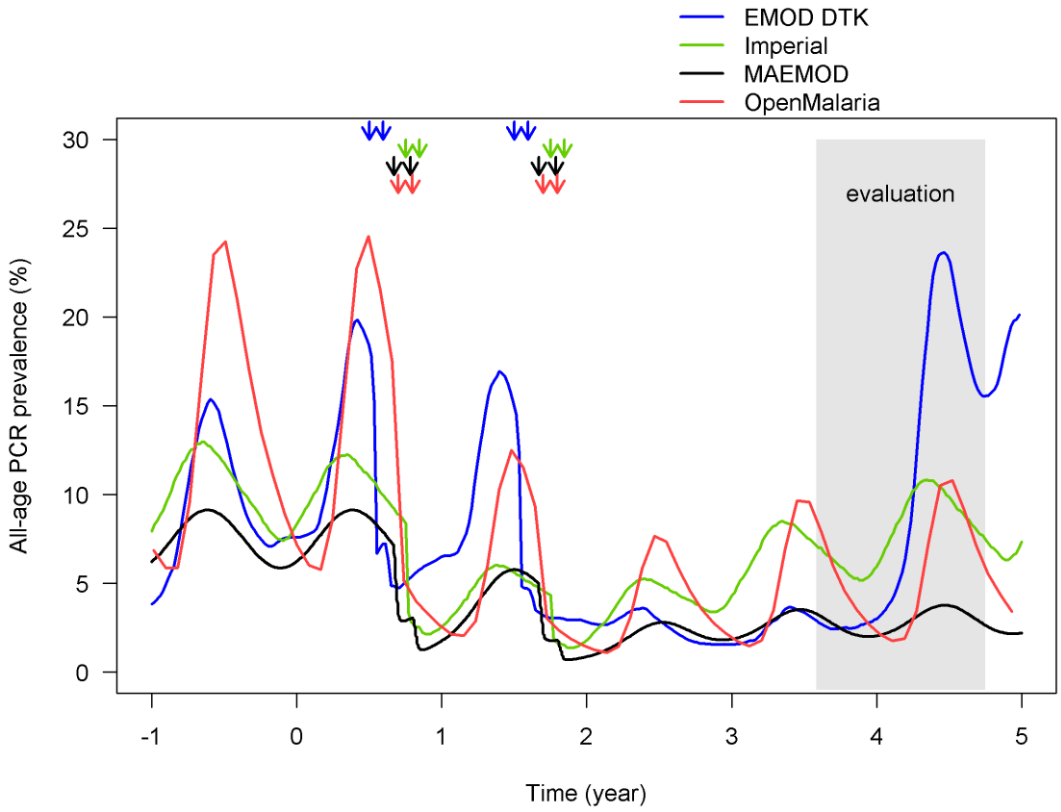

Figure 1 Example simulated output from three different models

The timing of each MDA round in each model is shown by coloured arrows. The four different models show the output under the baseline scenario (coverage = 70%, 2 years of MDA, 2 rounds per year, 5 weeks between rounds, seasonal transmission (based on Zambia), mean annual prevalence pre-intervention by microscopy in 2-10 year olds (PfPR2-10) = 5%.

Size of MDA impact: model comparison

While the four different models all show similar trends in the impact of MDA over time (Figure 1), in terms of an initial rapid reduction in $Pf PR_{PCR}$ followed by a rebound in transmission, substantial differences can be observed in both pre-intervention transmission and the predicted magnitude of MDA impact in the baseline scenario (Figures 1 and 2). EMOD DTK and MAEMOD

predict the largest % reduction in *Pf*PR$_{PCR}$ of 64%, OpenMalaria the next largest at 58% reduction, and Imperial the smallest at 19% reduction.

There are many differences in assumptions between the models which cause the differences in resilience shown in Figure 1, for example, the pre-intervention PCR prevalence which is determined by the assumed relationship between slide-prevalence and PCR prevalence, the relationship between EIR, prevalence and the basic case reproduction number (R_0), the assumed degree of heterogeneity in exposure of the population to mosquito bites, the impact of ongoing case management, the degree of stochastic variability in the model and the dynamics of immunity (see Appendix and the Discussion for more details on model assumptions). We did not undertake a formal analysis to quantify the absolute or relative impact of these assumptions on the outcomes due to time constraints.

There are many differences in assumptions between the models which could cause these differences and these are listed in the Appendix as well as in the discussion section. Despite these differences between the size of impact predicted by the different models, we found generally greater agreement as to the relative impact of different operational characteristics of MDA in different transmission settings. These findings are detailed below.

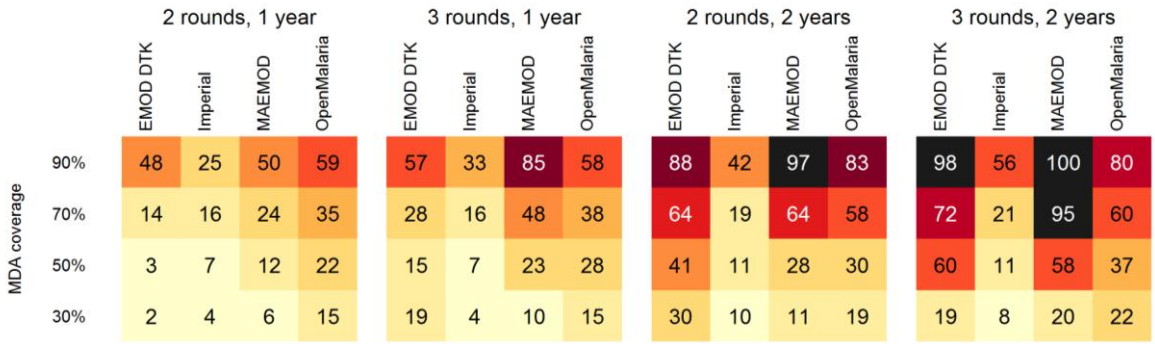

Figure 2 Percentage reduction in mean annual all-age PCR prevalence (PfPRPCR) in 3rd year after the intervention has ended. Darker colours indicate larger reductions.

Programmatic factors

Effective coverage

Effective coverage has a large impact on *Pf*PR$_{PCR}$ percentage reduction in all the models. For example, the median estimated % reduction in *Pf*PR$_{PCR}$ 3 years after 2 rounds of MDA within a year spaced 5 weeks apart at 30% coverage is 5% (range across models 2-15%), while the median impact at 70% coverage is 20% reduction (range 14-35%) (Figure 2).

Overlap in coverage between rounds

When multiple rounds of MDA are carried out, all the models show that coverage overlap (whether the same or different individuals participate in each round) has a significant impact on MDA effectiveness due to its direct influence on overall effective coverage. For example, if participation was entirely random in each round, 2 rounds of MDA at 70% coverage would mean that approximately 90% of the population would receive one or more treatment courses. At the other extreme, however, if exactly the same individuals participated in each round, then 2 rounds at 70% coverage would still only reach 70% of the population (Figure 3a). In reality, the situation is likely to be somewhere between the two extremes.

The models indicate that, with closely-spaced rounds of treatment (such as the 4-6 week intervals considered in the scenarios here), the most important operational factor determining MDA impact is the proportion of the population who do not receive any MDA treatment in any rounds (Figure 3b). This can be reduced by either high per-round coverage or through reaching different individuals in additional MDA rounds in the same year. Figure 3b shows the close relationship between the proportion of the population not receiving treatment in any round, and MDA impact in the OpenMalaria model. This relationship was examined in the EMOD DTK and Imperial models and the same conclusions were drawn (results not shown).

Coverage overlap in MDA rounds with a long gap between them (*e.g.* 2 years of MDA with 1 round per year) is predicted to be less important for MDA impact. This is because sufficient time has elapsed for many individuals taking part in the first round of MDA to become reinfected (assuming transmission is not extremely low or interrupted in year 1). As prevalence declines, however, the models suggest coverage overlap in different years may become more important, especially in longer MDA programmes.

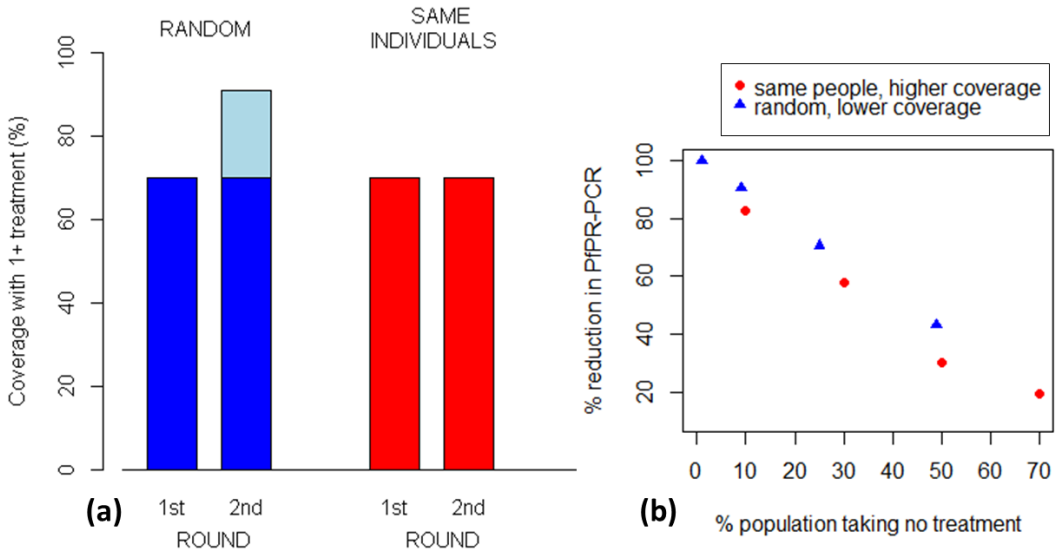

Figure 3 Overlap in coverage between MDA rounds and impact on PfPRPCR. (a)

The proportion of the population receiving 1 or more treatment courses after 2 rounds of MDA, each at 70% coverage with either random participation or the same individuals participating each time. (b) % reduction in *Pf*PR_{PCR} 3 years after MDA according to the % population not receiving treatment in any rounds in the baseline scenario. Blue dots represent two rounds of MDA randomly targeted at 30%, 50%, 70% and 90% coverage while red dots represent the same two rounds of MDA but where the same individuals are treated each round. Results shown are from the OpenMalaria model.

Number of rounds

The impact of 2 versus 3 rounds per year depends on what extent the additional round reaches individuals not covered in the first round, as described above. If exactly the same individuals participated in each round of MDA, as assumed in the EMOD DTK, Imperial and OpenMalaria baseline simulations, having a third round made negligible difference to the outcome in any of the models when the rounds were spaced 4-6 weeks apart (Figure 2). If the people treated in each round were a random selection, as in the MAEMOD model, then the efficacy of 3 annual rounds was greater than that of 2 rounds in all scenarios (Figure 2 and 3).

Interval between rounds

In all the models, there was minimal difference in MDA impact when within-year MDA rounds were spaced 4, 5 or 6 weeks apart (Figure A1, Appendix). The Imperial, MAEMOD and

OpenMalaria models estimated that in the scenario with 3 rounds of MDA per year for 1 year at 70% coverage and 5% pre-intervention *Pf*PR_{2-10}, the median % reduction in *Pf*PR_{PCR} 3 years later was 36% (range 12-47%) with 4-week spacing and 37% (20-47%) with 6 week spacing. The same result was found across every transmission setting examined in this exercise (baseline PfPR_{2-10} 1%, 5% or 10%, and in seasonal and non-seasonal settings). The insensitivity of the results to these changes in spacing is due to the fact that reinfection rates between rounds are low over the course of 4-6 weeks, because of the low transmission and long post-treatment prophylaxis in the scenarios considered here.

Duration of intervention

Prevalence remains lower for a longer period with a 2-year MDA campaign than a 1 year MDA campaign. Based on *Pf*PR_{PCR} outcomes 3 years after the end of the *last round* of MDA, all the models found some greater impact of a longer duration of MDA (Figure 2). In the baseline scenario, there was a median % reduction in *Pf*PR_{PCR} of 61% (range 19-64%) after 2 years of MDA and 20% (14-35%) after 1 year.

Addition of Primaquine to ACT MDA

The four models are, in most scenarios, aligned that adding primaquine to an ACT only increases the MDA impact further by a small amount. The reduction in *Pf*PR_{PCR} was increased by a range of <1% to 8% in the MAEMOD and Imperial models, in agreement with previous OpenMalaria modelling results for southern Zambia, which found this intervention had negligible effect (7). EMOD DTK, however, did find in previous work in higher transmission settings that primaquine added to artemether-lumefantrine increased relative impact on *Pf*PR_{PCR} by a modest 13% and could increase the impact by up to 50-60% when added to DHA-piperaquine (5).

The generally low impact predicted in the models is because, in the data used to parameterize the models, ACTs are already so effective at preventing onward transmission without primaquine that, in the simulations, most transmission after the MDA has ended arises from those who did not participate in the MDA, not from those who were treated. However, the EMOD DTK model found a greater effect of DHA-piperaquine + primaquine because the combination of a long-acting and a highly gametocytocidal drug meant that a proportion of the population was effectively stopped from participating in transmission for a period of weeks. The other models did not find this, and was likely due to different assumptions about how effective DHA-piperaquine is at preventing onward transmission without primaquine.

These results are based on data from areas with artemisinin-sensitive parasites. Previous modelling by MAEMOD has shown that primaquine has a slightly greater additional effect in the presence of artemisinin resistance (8). For example, when 0% of infections are artemisinin-resistant, MAEMOD estimates that adding primaquine to an ACT in an MDA done at 70% coverage will increase the reduction in *Pf*PR_{PCR} by 5%, and when 10% of infections are artemisinin-resistant, primaquine increases the reduction to 6.2%.

Replacing vector control with MDA

The use of MDA in the context of removal of vector control was explored using the OpenMalaria model. This was modelled as a tenfold increase in the emergence rate of adult mosquitos starting at the beginning of 2015, which is followed by the baseline programme of MDA (coverage = 70%, 2 years of MDA, 2 rounds per year 5 weeks between rounds, seasonal transmission (based on Zambia), mean prevalence pre-intervention by microscopy in 2-10 year olds (*Pf*PR_{2-10}) = 5%).

The removal of vector control led to a sudden and large increase in all-age prevalence, and the subsequent MDA programme did very little to reduce this shift even in the short term. We predict, therefore, that an MDA programme of this type is insufficient to totally replace vector

control, even at high levels of coverage. A separate report has been submitted for the September MPAC meeting on simulating the effects of scaling back vector control, which includes a more detailed analysis of replacing vector control with mass screen and treat interventions (9).

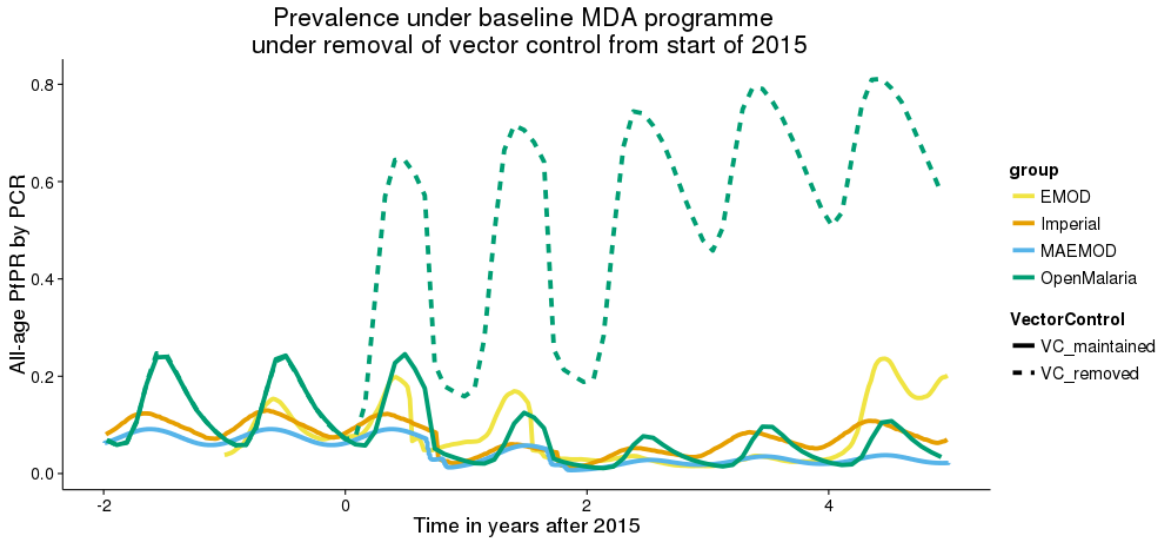

Figure 4 Predicted impact of replacing vector control with MDA

All-age *Pf*PR$_{PCR}$ prevalence over time. The dashed line shows prevalence in the OpenMalaria model scenario where vector control is removed at the start of 2015 and an MDA programme is begun later that year. For comparison, the unbroken lines show the equivalent scenarios from the OpenMalaria and Imperial models where the same MDA programme is carried out in the context of maintained vector control.

Setting-dependent factors

Baseline transmission intensity

All the models show that the impact of MDA is highly sensitive to the pre-intervention prevalence (Figure 5). Areas of low prevalence will experience a much greater impact (in terms of percentage reduction in prevalence). This is because low transmission settings are less resilient, *i.e.* transmission takes longer to rebound. In a stochastic model framework, all models predict that elimination is possible with MDA in very low prevalence settings (~1% *Pf*PR$_{2-10}$) in a proportion of simulations.

In a higher prevalence setting (10% *Pf*PR$_{2-10}$), the percentage reduction in *Pf*PR$_{PCR}$ is considerably lower than for a setting with 5% prevalence. We predict that even with high coverage (90%), three rounds per year and 2 years of intervention, *Pf*PR$_{PCR}$ 3 years later will only be reduced by a median of 48% (19-95%) from its pre-intervention level, compared to 80% (56-100%) in the setting with 5% baseline prevalence. However, the percentage point reduction in prevalence – *i.e.* the absolute reduction – is greater in higher prevalence settings as more infections are being cleared. In these settings, MDA is less likely to eliminate but will have higher impact on burden if it is part of a long term scaled-up control programme.

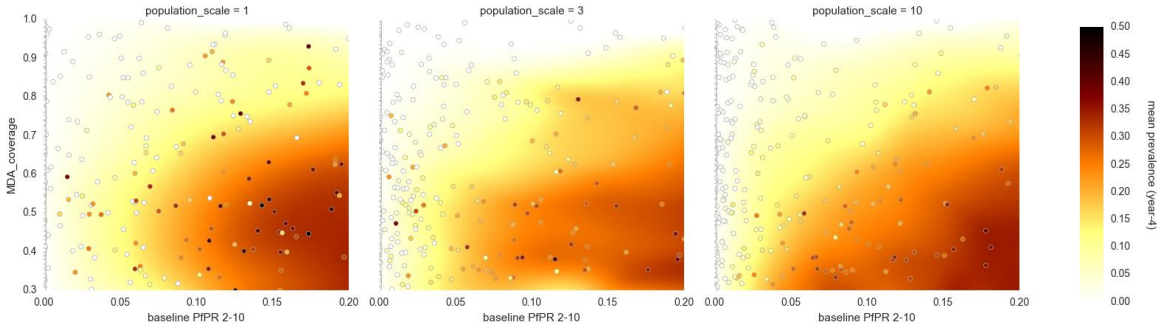

Figure 5 Impact of MDA in settings with different baseline transmission intensity and population sizes

The figure presents mean prevalence 3 years after the baseline MDA programme (Table 1) from 100 stochastic simulations in populations of 1,000 (left), 3,000 (middle) and 10,000 (right) individuals. Results shown are from the EMOD DTK model; similar trends were seen in other models.

Importation

OpenMalaria and EMOD DTK simulated ongoing importation during MDA at rates of 0.4-1.6 infections per 10,000 people per year, based on data from Zanzibar (10). In the baseline scenario of 5% $PfPR_{2-10}$, imported cases occurring at this rate are a very small proportion of the total existing infections in the population, and therefore the results are not sensitive to importation (Figure 6). Our baseline assumption of high access to treatment also means that many imported cases are treated before transmitting onwards. However when $PfPR_{2-10}$ is lower, or in a scenario where MDA has eliminated transmission or brought it to a very low level, imported cases would constitute a much larger proportion of cases and would be instrumental to increasing transmission.

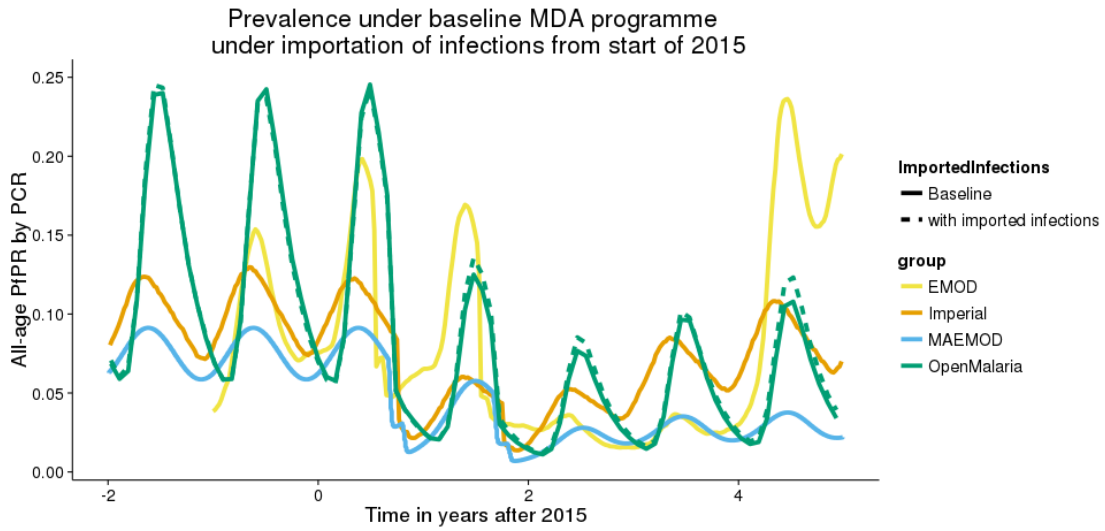

Figure 6 Predicted impact of imported infections

All-age *Pf*PR_{PCR} prevalence over time. The dashed line shows prevalence in the OpenMalaria model scenario where imported infections are introduced at the start of 2015 at the rate of 1.6 infections per 10,000 people per year. The baseline MDA programme is begun later that year at 70% coverage. For comparison, the unbroken lines show the equivalent scenarios from the OpenMalaria and Imperial models where the same MDA programme is carried out with no importation of infections.

Population size

MDA more easily causes stochastic extinction in smaller simulated populations, and there is greater simulation-to-simulation variability. Example model output is shown from EMOD DTK (Figure 5). The other stochastic models (OpenMalaria and Imperial) show the same trend in results.

Optimal timing

Following the findings of other simulation studies (2, 3, 8, 11, 12), we simulated MDA in the dry season to represent optimal timing. With the Imperial model this resulted in lower subsequent prevalence than MDA applied in the wet-season.

In an area with highly seasonal transmission, conducting MDA at the optimal time will increase the effectiveness of the intervention. For example, at 70% coverage the average reduction in *Pf*PR_{PCR} is estimated by the Imperial model to be approximately 1.45 times larger 3 years after conducting MDA at the end of the rainy season (April) compared to the *Pf*PR_{PCR} reduction expected after conducting MDA at the beginning of the rainy season (November) (Figure 7). For OpenMalaria, this effect is not as pronounced but is more visible at high coverage. For MAEMOD, the timing affected the magnitude of the initial drop in prevalence immediately following a round of MDA, the optimal timing being halfway between the peak and trough in prevalence, but timing had little effect on the longer term reduction. The optimal time for MDA in a setting with two rainy seasons, such as seen in East Africa, was examined in the Imperial model. Because transmission is more evenly spread over the year in such settings, there is considerably less effect of MDA timing. At a given average baseline slide prevalence level, MDA is predicted to be marginally more effective in a seasonal setting compared to a non-seasonal setting (assuming the MDA is conducted at the optimal time).

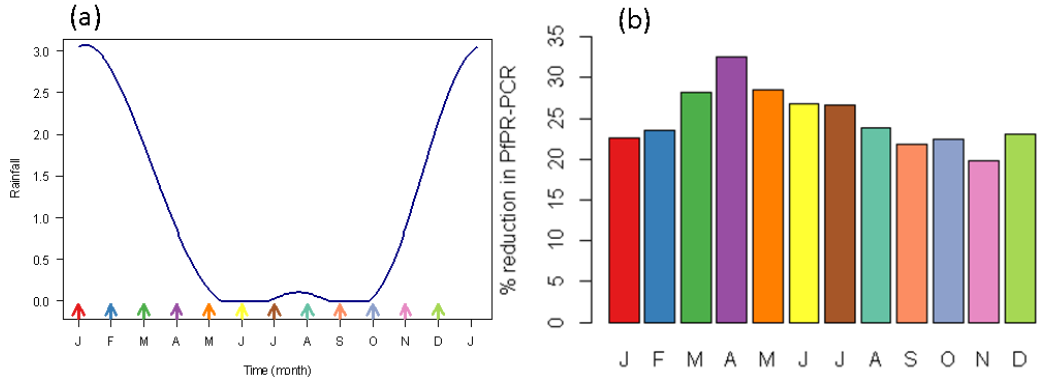

Figure 7 Optimal timing in the Imperial model

(a) smoothed annual rainfall pattern (b) % reduction in *Pf*PR_{PCR} from baselines.

Artemisinin resistance

MAEMOD has been used to simulate ACT-based MDA in the presence of artemisinin resistance. These results indicate that MDA to some extent speeds up the selection of resistant strains (Figure 8), but this effect is not very large because there is already a significant selection pressure from the case management of symptomatic cases.

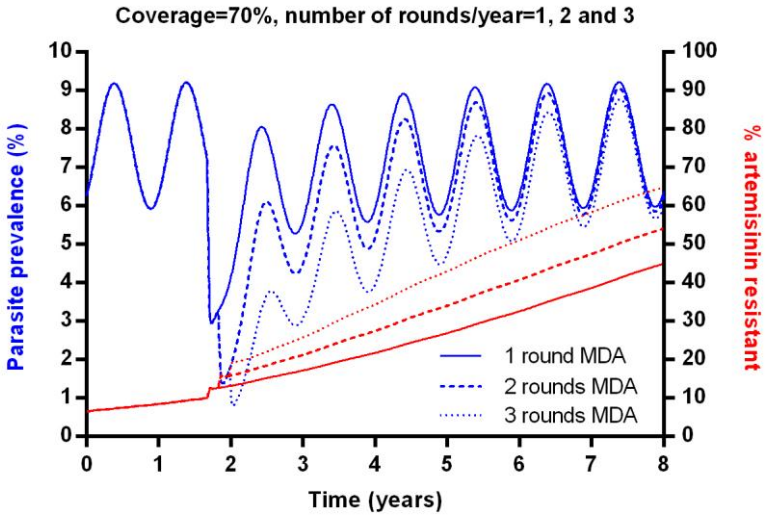

Figure 8 Impact of MDA with ACT on malaria prevalence and the % of artemisinin resistant parasites

Discussion

While individual models may show different magnitudes of overall impact, there is substantial consensus among the models on which factors have the greatest influence on impact, including both the characteristics of the MDA program and the transmission setting in which it is applied.

Percentage reductions are highest with low transmission settings, longer duration programmes and low simulated population sizes. Importation rates, the spacing between rounds and the addition of primaquine to MDA with long lasting ACTs have little effect within the scenarios examined here. The proportion of the population reached by at least one MDA round per year has a very large influence on MDA effectiveness and should be the focus of operational efforts.

This exercise did not entail formal analysis of which differences between the models account for the variation in predicted impact of MDA. MDA can have an intense impact on transmission, at least in the short-term, making the transmission dynamics more complex than those analysed in the recent in-depth comparisons of models of RTS,S effects (13). Differences between the models in basic epidemiological quantities including duration of untreated infections and clinical immunity, may be relevant but have not generally been critically evaluated. For instance OpenMalaria simulates higher levels of acute illness in naïve hosts than does the Imperial model, and this means that if (as in these simulations), there is good access to care, low prevalence in OpenMalaria corresponds to higher force of infection, but less stable transmission than at lower coverage of case management.

A further source of variation between the models regarding impacts is the differences in assumptions about within-population heterogeneity in prevalence, which were not standardised in this exercise. In some of the models, as in reality, an average prevalence of 1% can only be maintained by simulating variability in susceptibility and/or response to infection between different hosts. Some of this is variation in space, but the models also address non-spatial variation in susceptibility between hosts in different ways. The extent of these sources of variability is critical for the stability of transmission. Temporal (seasonal) variation makes transmission less stable, at a given level of prevalence, while spatial

heterogeneity can make it more stable. Population sub-division may also be critically important. If there are many areas with zero prevalence and a few smaller areas with higher prevalence, simulations of small populations with 5-10% prevalence, diluted by unexposed individuals may be appropriate representations of 1% average prevalence. The size of such sub-populations (and their degree of interconnection, corresponding to the frequency of importations) can then be crucial, since stochastic extinction is much more likely in smaller populations.

Each model fixed the initial prevalence values for their simulations, but this could correspond to very different settings in terms of the immune status of the human population, the pattern of vectorial capacity, and correspondingly whether this represents long-term stable transmission, recent infection of a receptive human population, or the result of a temporary fluctuation in receptivity. Where an initial stable endemic state was used, this approximates only a subset of the settings where MDA might be considered. It does not consider epidemics: either where non-immune populations (such as displaced people) move into areas of high vectorial capacity, or where vectorial capacity temporarily increases (*e.g.* owing to unusual weather patterns). Some initial conditions lead to extinction of the parasite population even without MDA. It is then questionable whether there can be an incremental benefit of MDA. This may correspond to the reality in some epidemic situations, but there is an unanswered challenge in how to distinguish such settings in practice from others where MDA may make a critical difference.

The value of the present simulations is therefore mainly to show that there is a consensus on the relative influence of MDA operational characteristics. This states that reaching as many people as possible at least once should be the operational priority, whether this is achieved through high per-round coverage, multiple rounds that target different individuals, or optimising timing between rounds to treat different individuals. It should be noted that, under no circumstances do any of the models predict that MDA is an effective replacement for existing vector control and indeed the overarching message from this model comparison is that without some other change, such as improved vector control, the effects of MDA are likely to be transient.

The challenges in comparing the models would be even greater for formal comparisons of interruption of transmission than for reductions in prevalence, since uniform extinction criteria are not applicable given the difference in model structures. The quantitative predictions of impact are associated with substantial model uncertainty.

Future work may address these non-harmonised factors between the models and aim to give more comparable estimates of impact magnitude. Predictions of transmission interruption will also be developed by applying these models in standardised explicitly spatial contexts based on local epidemiological data and realistic operational constraints.

Appendix: Summary of models of malaria transmission.

Model name	EMOD DTK	Imperial	MAEMOD	OpenMalaria
Institutional home	Institute for Disease Modelling (IDM)	Imperial College London (IC)	MORU	Swiss Tropical and Public Health Institute (Swiss TPH)
Type of model & references	Individual-based stochastic microsimulation (14, 15)	Individual-based stochastic microsimulations of malaria in humans linked to a stochastic compartmental model for mosquitoes (16)	Deterministic compartmental model described by differential equations (8) including drug action on each stage of the infection	Single location individual-based simulation of malaria in humans (17) linked to deterministic model of malaria in mosquitoes (18)
How infections are tracked	Tracks parasite densities of different surface-antigen types	Tracks membership of categories of infection (symptomatic, asymptomatic, submicroscopic, treated)	Tracks membership of categories of infection	Tracks parasite densities corresponding to different infection events
Relationship between EIR and prevalence	Immunity is acquired through cumulative exposure to different antigenic determinants (19) with heterogeneity in individual biting rates included	Immunity is acquired through cumulative exposure mosquito bites with heterogeneity in individual biting rates included	Subdivides population into non-immune & immune classes	Sub-models of infection of humans (20), and of blood-stage parasite densities with main immune effects controlling parasite densities (21)
Duration of infections	Infection duration based on malariatherapy (19) and cross-sectional survey data (22)	Infection duration based on fitting to asexual parasite prevalence data by age, transmission intensity & seasonality	Infection duration based on malariatherapy data and data from endemic areas	Infection duration based on malariatherapy data (21)
Impact of MDA or case management	Reduces blood-stage parasite densities according to age- and dose-specific PkPd (5) with the corresponding clearance and prophylactic effects. Prophylactic period based on PkPd studies (5)	Truncates infections and has subsequent prophylactic effect based on fitting pharmacokinetic/dynamic models to field studies	Post-treatment prophylactic period derived from field studies of time to next infection	Truncates infections, and has subsequent prophylactic effect based on pharmaco-kinetic/dynamic studies
Validation against MDA or MSAT trials	Evaluated against MACEPA MSAT	Evaluated against a controlled MDA	Fitted to an MDA trial in Cambodia	Fitted to the data of the Garki

	trial in Southern Zambia (unpublished)	trial (23) in Burkina Faso (model slightly optimistic about impact vs data), and the MACEPA MSAT trial in Southern Zambia (model matched data)	(24)	project (Matsari) (20), and evaluated against the MACEPA MSAT trial in Southern Zambia (7)
Infectiousness to mosquitoes	A function of mature gametocyte density and cytokine densities (19, 22)	Related to asexual parasite dynamics and lagged to allow for development of gametocytes	Infected individuals have a constant infectiousness	Lagged function of asexual parasite density (25)
Heterogeneity in exposure	Age-dependent biting (26) and configurable distribution of household-variability (the latter disabled in this analysis)	Included	Not included	Included
Initial state	-	Back-calculating required mosquito density to achieve given initial prevalence at an approximate steady state in the presence of treatment and LLIN	Set transmission rate to achieve given initial prevalence at an approximate steady state in the presence of treatment	Back-calculating required mosquito density to achieve given initial prevalence at an approximate steady state in the presence of treatment
Source of seasonality pattern	Rainfall and imputed temperature (27) driving larval habitat model fitted to clinical incidence patterns in Sinazongwe and Gwembe Districts	Rainfall data from Zambia combined with larval & adult mosquito model	Same EIR input as Imperial model	Based on pattern for southern Zambia used by (7)
Age structured model	Yes	Yes	No	Yes
Simulation of correlated rounds of intervention	Yes	Yes	No	Yes

The table summarises the characteristics and functionality of the models as applied in this exercise. The ACT modelled for this exercise was DHA-piperaquine. It was assumed that no antimalarial drug resistance was present throughout the modelled period. All the models are extensible to include other functionality (*e.g.* different drugs, effects of drug resistance, impact on drug resistance, vector bionomics and details of vector control, different initial conditions, other concomitant interventions). A detailed comparison of EMOD DTK, Imperial and OpenMalaria, including references to the data to which they are fitted, is available in a forthcoming paper on RTS,S (13).

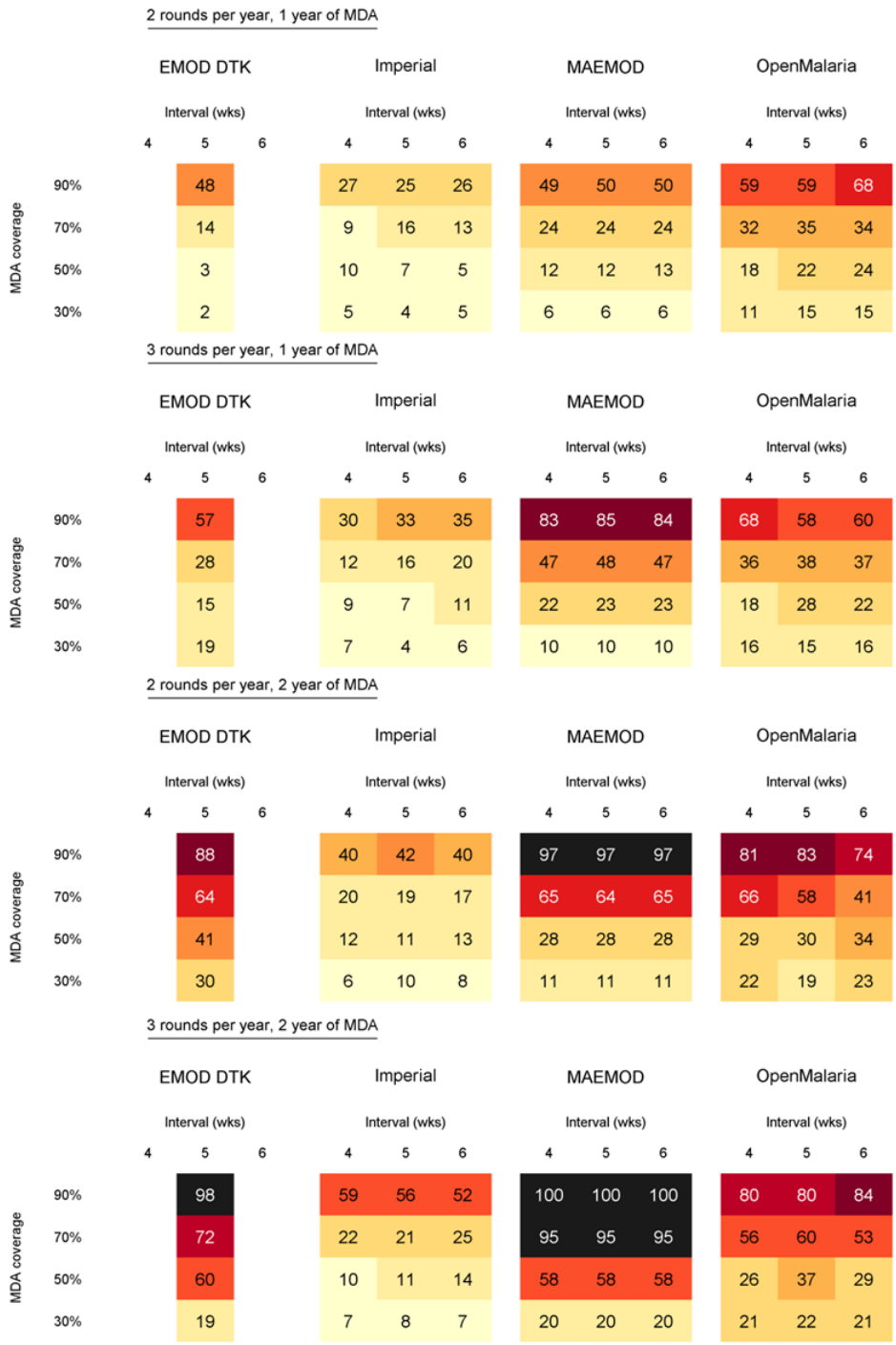

Figure A1 Percentage reduction in mean annual all-age PCR prevalence (PfPRPCR) in 3rd year after the intervention has ended

Darker colours indicate larger reductions. This figures summarises the same results as Figure 2 in the main text, but with results shown for the interval (in weeks) between MDA rounds.

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GLOBAL MALARIA PROGRAMME

World Health Organization

Evidence Review Group on MDA, MSAT and FSAT

Malaria Policy Advisory Committee
Geneva, Switzerland
16-18 September 2015

Kevin Marsh
Chairperson of the Evidence Review Group

Outline of the Presentation

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

Additional work completed after the meeting of the ERG on MDA

Background

- WHO Technical Consultation held in 2003 concluded there was little evidence that MDA is effective in reducing transmission although a reduction in parasite prevalence and transient reduction in mortality and morbidity were documented in some cases.

- WHO consultation In 2010 reviewed the potential role of MDA to eliminate multi-drug resistance and recommended immediate planning of a pilot MDA operation in western Cambodia or eastern Thailand.

- Cochrane review 2013 concluded that MDA appears to quickly reduce malaria parasitaemia and several clinical outcomes, but more studies are required to assess the impact after 6 months, the barriers for community uptake and the potential contribution to the development of drug resistance.

Rationale for Review

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

Objectives of the ERG on MDA/MSAT/FSAT

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

Conclusions - Available Literature

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

Key Conclusions - MDA in Oncho and Filariasis

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

Key Conclusions - Ebola in Sierra Leone

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

Key Conclusions - Asymptomatic Reservoir Thailand and Vietnam

- MDA combined with PQ, concurrently implemented with vector control in mainland moderate transmission regions resulted in a decrease in parasite carriage, but did not eliminate the transmission reservoir.

- Similarly, efforts to reduce parasite positivity through TME appear to have been constrained by pressure of imported cases from the forest and neighbouring countries.

Key Conclusions - Islands

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

Key Conclusions - MPPT for P vivax

- MPPT was safely deployed at a large scale with low reporting of AEs in a region with a well-developed primary health-care system and low prevalence of G6PD deficiency.

- Although the number of cases was significantly reduced, it was not possible to interrupt *P. vivax* transmission through the use of MPPT; using vector control might have helped to reach this goal.

Key Conclusions - MSAT and FSAT

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

ERG was asked to address these questions

First individually ….

Should MDA/MSAT/FSAT be recommended to interrupt transmission ….

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

..and then in 4 working groups

Should MDA/MSAT/FSAT be recommended to reduce transmission ….

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

Proposed recommendations (I)

1. Use of MDA to interrupt transmission of falciparum malaria can be considered in endemic island communities and in low-endemic non-island settings approaching elimination, where there is minimal risk of re-introduction of infection, good access to treatment, and implementation of vector control and surveillance.

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

Mass drug administration in areas of low malaria prevalence

Patient or population: People living in malaria endemic areas
Settings: Areas with low (≤5%) prevalence
Intervention: Mass drug administration (any regimen)
Comparison: Placebo or no intervention (or baseline data in before-and-after studies)

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

The **assumed risk** has been set at 5%. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio.

[1] For illustrative purposes the control group prevalence has been set at 5%.
[2] Downgrade by 1 for serious risk of bias: This single study is an uncontrolled before and after study, and so at very high risk of confounding.
[3] Downgraded by 1 for serious indirectness: This 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.

Proposed recommendations (II)

3. Use of MDA to rapidly reduce malaria morbidity and mortality can be considered for epidemic control as part of the immediate response, while other interventions are put in place.

4. Use of MDA to reduce malaria morbidity and mortality can be considered during exceptional circumstances, where the health system is overwhelmed and unable to serve the affected communities.

Proposed recommendations (III)

5. There is insufficient evidence to provide guidance on use of MDA in settings with moderate or high transmission; more research is required to inform future recommendations.

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

General Considerations 1

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

General considerations 2

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

What can results from modeling add?

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

Imperial College, London	Swiss TPH, Basel	IDM, Seattle	MORU, Bangkok

Approach taken

Sensitivity of MDA impact to changes from a baseline scenario:

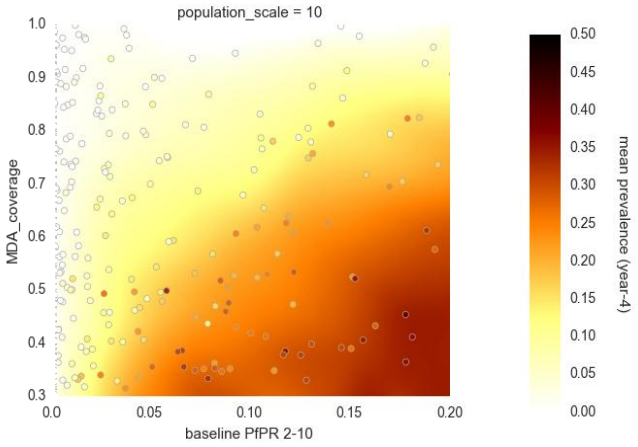
1. Key operational variables analysis
   - Coverage, round interval, number of rounds, duration of program
2. Effects in different context
   - Endemicity, seasonal timing, population size, imported infections
3. Primaquine analysis
   - Presence or absence of low dose primaquine to MDA with long lasting ACTs

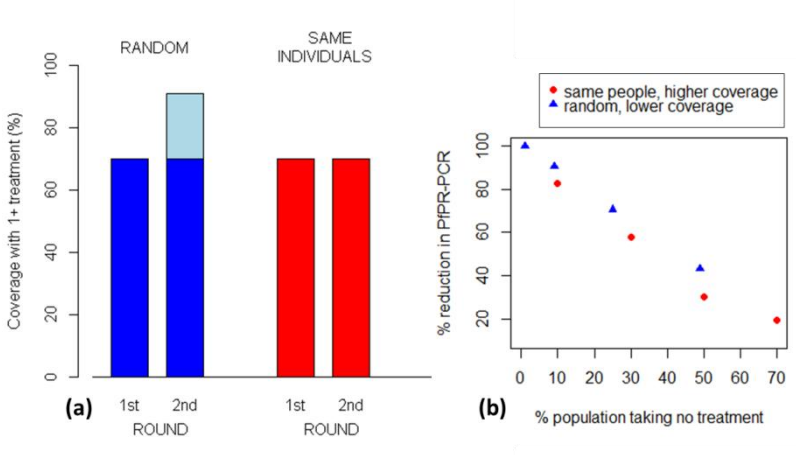
Baseline scenario	
Rounds per year	2
Effective coverage	70%
Coverage correlation	1
Round interval	5w
Programme duration	2y
Drug choice	DHA-PQP
Endemicity	5% *Pf*PR_{2-10}
Population size	10,000
Seasonality	Zambia-like

Key recommendations

MDA predicted to be effective

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





Reaching unique individuals

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

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

World Health Organization

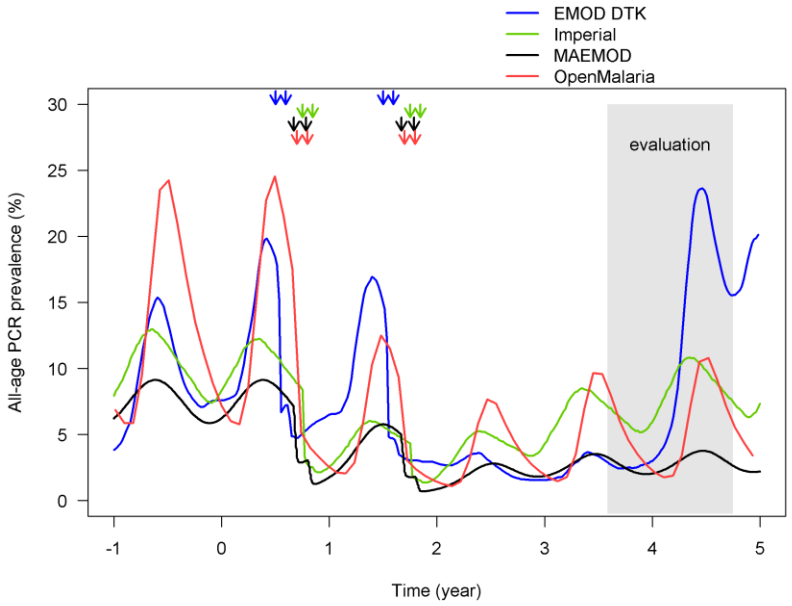
Global Malaria Programme

Effect of other factors on MDA impact

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

Limitations of these analyses

- Models not fully harmonized
  - All show similar patterns, but vary in magnitude of predicted effect
  - Can be due to different assumptions, or different interpretations of the baseline
  - A full harmonization to understand these differences (like for RTS,S) takes much longer



- Limited ability to predict transmission interruption
  - Assumptions about large well mixed populations unrealistic close to elimination

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

MDA cost analysis

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

MDA cost (in 2015 US$)

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

Figure 1: MDA delivery cost breakdown in Comoros

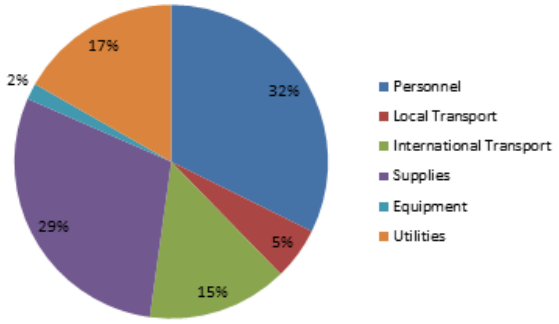


Figure 2: MDA delivery cost breakdown in Vanuatu

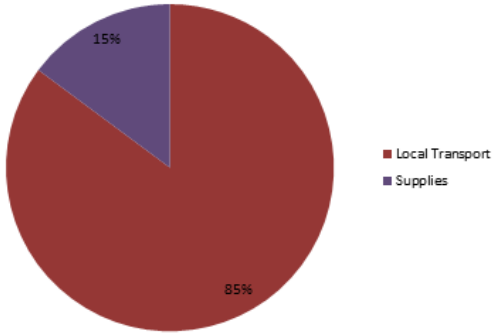
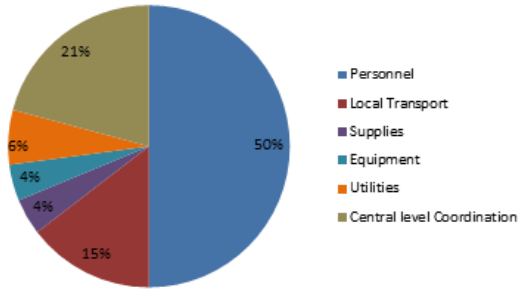


Figure 3: MDA delivery cost breakdown in Sierra Leone (Western areas)



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

Proposed recommendations (I)

1. Use of MDA to interrupt transmission of falciparum malaria can be considered in endemic island communities and in low-endemic non-island settings approaching elimination, where there is minimal risk of re-introduction of infection, good access to treatment, and implementation of vector control and surveillance.

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

Proposed recommendations (II)

3. Use of MDA to rapidly reduce malaria morbidity and mortality can be considered for epidemic control as part of the immediate response, while other interventions are put in place.

4. Use of MDA to reduce malaria morbidity and mortality can be considered during exceptional circumstances, where the health system is overwhelmed and unable to serve the affected communities.

Proposed recommendations (III)

5. There is insufficient evidence to provide guidance on use of MDA in settings with moderate or high transmission; more research is required to inform future recommendations.

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

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
WHO Headquarters, Geneva 20–22 April 2015

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.

WHO/HTM/GMP/MPAC/2015.9

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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Global **Malaria** Programme

The role of mass drug administration, mass screening and treatment, and focal screening and treatment for malaria

NOVEMBER 2015

RECOMMENDATIONS

Over the past decade, mass drug administration (MDA) and other approaches to mass screening and treatment have received increasing interest in the context of malaria elimination and, more recently, in emergency situations such as the Ebola epidemic in West Africa. MDA consists in the administration of a full dose of antimalarial treatment, irrespective of the knowledge of symptoms or presence of infection, to an entire population in a given area, except those in whom the medicine is contraindicated. Mass screening and treatment (MSAT) and focal screening and treatment (FSAT) for malaria require testing all people in a broad or defined geographical area and treating only positive cases.

MDA is conducted in a coordinated manner, so that the drug is taken at approximately the same time by the whole population at risk, often at repeated intervals. The objectives of MDA can be to reduce or interrupt transmission, to rapidly reduce malaria morbidity and mortality, or to prevent relapses and resulting malaria transmission.

In the context of transmission reduction, MDA aims to provide therapeutic concentrations of antimalarial drugs to as large a proportion of the population as possible in order to cure asymptomatic infections and to prevent re-infection during the period of post-treatment prophylaxis. To impact on transmission, MDA requires high coverage of the target population which, in turn, demands a high level of community participation and engagement.

MDA rapidly reduces the prevalence and incidence of malaria in the short term. However, if the transmission of malaria is not interrupted or its importation not prevented, transmission eventually returns to its original level once MDA is terminated, unless the vectorial capacity is reduced and maintained at a very low level during the post MDA period. If malaria is not eliminated, MDA may provide a significant selective pressure for the emergence of drug resistance, particularly in the case of *Plasmodium falciparum*. For this reason, it should not be started unless there is a good chance that elimination is feasible in the area where it is being administered.

World Health Organization

Exceptions to this are when MDA is used in emergency situations where the primary aim is to prevent morbidity and mortality rather than interrupt transmission. In some circumstances (e.g. elimination of multidrug-resistant *P. falciparum*), elimination of only one species may be the objective.

RECOMMENDATIONS

Based on a recent evidence review (*1*), 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.
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.
7. Mass screening and treatment and focal screening and treatment for malaria are not recommended as interventions to interrupt malaria transmission.
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. Programmes 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.

REFERENCES

1. The report available on the WHO-GMP website at http://www.who.int/malaria/mpac/mpac-sept2015-erg-mda-report.pdf

WHO/HTM/GMP/2015.8

Malaria Policy Advisory Committee Meeting

16–18 September 2015, Geneva, Switzerland
Background document for Session 2

Considerations for implementation of G6PD testing and radical cure in *P. vivax* endemic countries

August 2015, Geneva, Switzerland

Background

The current WHO *Guidelines for the treatment of malaria* (*1*) contain recommendations for the treatment of *Plasmodium vivax* and *P. ovale* (see Box 1A and Box 1B). These recommendations are based on the need to radically cure patients using primaquine (the only available anti-relapse medicine) while at the same time minimizing the risk of primaquine-induced acute haemolysis in those who are deficient in the enzyme glucose-6-phospate dehydrogenase (G6PD). The guidelines recommend that patients with confirmed *P. vivax* or *P. ovale* malaria who are not aware of their G6PD status be tested before the administration of radical cure with primaquine. However, given the limited availability of field-adapted G6PD tests and some performance limitations with those tests, a decision to administer or withhold primaquine may still have to be based on weighing the benefits of radical cure against the haemolytic risk posed by primaquine.

Box 1 A. Recommendations in the WHO *Guidelines for the treatment of malaria* (*1*)

Preventing relapse in *P. vivax* or *P. ovale* malaria

The G6PD status of patients should be used to guide administration of primaquine for preventing relapse.
Good practice statement

To prevent relapse, treat *P. vivax* or *P. ovale* malaria in children and adults (except pregnant women, infants aged < 6 months, women breastfeeding infants aged < 6 months, women breastfeeding older infants unless they are known not to be G6PD deficient, and people with G6PD deficiency) with a 14-day course (0.25-0.5 mg/kg bw daily) of primaquine in all transmission settings.
Strong recommendation, high-quality evidence

In people with G6PD deficiency, consider preventing relapse by giving primaquine base at 0.75 mg/kg bw once a week for 8 weeks, with close medical supervision for potential primaquine-induced haemolysis.
Conditional recommendation, very low-quality evidence

When G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of adding primaquine.
Good practice statement

Pregnant and breastfeeding women

In women who are pregnant or breastfeeding, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed, then, on the basis of G6PD status, treat with primaquine to prevent future relapse.
Conditional recommendation, moderate-quality evidence

WHO/HTM/GMP/MPAC/2015.11

Box 1 B Further guidance provided in the WHO Guidelines for the treatment of malaria (1)

- In patients known to be G6PD deficient, primaquine may be considered at a dose of 0.75 mg base/kg bw once a week for 8 weeks. The decision to give or withhold primaquine should depend on the possibility of giving the treatment under close medical supervision, with ready access to health facilities with blood transfusion services.
- Some heterozygote females who test as normal or not deficient in qualitative G6PD screening tests have intermediate G6PD activity and can still haemolyse substantially. Intermediate deficiency (30–80% of normal) and normal enzyme activity (> 80% of normal) can be differentiated only with a quantitative test. In the absence of quantitative testing, all females should be considered as potentially having intermediate G6PD activity and given the 14-day regimen of primaquine, with counselling on how to recognize symptoms and signs of haemolytic anaemia. They should be advised to stop primaquine and be told where to seek care should these signs develop.
- If G6PD testing is not available, a decision to prescribe or withhold primaquine should be based on the balance of the probability and benefits of preventing relapse against the risks of primaquine-induced haemolytic anaemia. This depends on the population prevalence of G6PD deficiency, the severity of the prevalent genotypes and on the capacity of health services to identify and manage primaquine-induced haemolytic reactions.

These recommendations on the radical cure of *P. vivax* infections are reiterated in *Control and elimination of Plasmodium vivax malaria – A technical brief* (*2*), a WHO publication that deals exclusively with the control and elimination of *P. vivax* malaria (see Box 2).

Box 2. Recommendations in Control and elimination of Plasmodium vivax malaria – A *technical brief* (*2*)

2.4.4 RECOMMENDATIONS

- Where feasible, all patients should be tested for G6PD deficiency before administering primaquine. Testing for G6PD deficiency in vivax malaria cases should be considered an integral part of ensuring universal access to diagnosis and treatment.
- G6PD testing should be incorporated into treatment guidelines, and services made available as tools are developed (possibly with referral of patients from lower to higher level health facilities).
- Where no G6PD test is available, it is difficult to generalize on the correct approach to patient management, because each individual assessment depends on the risk of adverse consequences (related to the likely dose of primaquine required, the prevalence and severity of G6PD deficiency in the area, the degree of anaemia and the availability of blood transfusion) and the potential benefits (related to the probability of relapse). In some circumstances, the assessment will favour withholding primaquine, and in others it will favour starting radical treatment after educating the patient about the possible risks, and informing the patient that they should stop the drug if they become ill or their urine becomes red or black.

The *P. vivax* recommendations were launched on 29 July 2015 at a global meeting held in New Delhi. The launch was followed by a 2-day meeting in which participating countries from all WHO regions other than the WHO African Region deliberated on the translation of the guidelines into policy and strategy in their programmes. As an outcome of those discussions, countries asked WHO to provide further guidance on how best to manage the challenging implementation issues they anticipate facing in an effort to comply with the recommendations for *P. vivax* radical cure. The main issues in implementation are the following:

- The limited availability of a robust, easy-to-use, point-of-care G6PD test restricts the ability to deploy primaquine for radical cure at lower levels of the health system. Promoting referral to higher level facilities will be problematic where referral services are weak (as is the case in most endemic countries) and it threatens early treatment of blood-stage infection if patients are referred to a higher level for both G6PD testing and *P. vivax* treatment.
- Some countries, particularly (but not only) in the Region of the Americas, are currently implementing radical cure for all patients at health facility level without necessarily testing for G6PD. This approach is justified on the basis that the G6PD deficiency allele frequency is very low (and the variants are generally considered to be mild) or absent, and therefore the benefits of providing radical cure for all *P. vivax* patients in whom the G6PD status is unknown exceeds the risk of primaquine-induced haemolysis. Hence, full compliance with the recommendation of testing before treatment could prevent expansion or could reverse implementation in settings where, before this recommendation, primaquine was being administered without first determining the G6PD status. In other settings, the risk–benefit analysis may be more challenging and guidance is needed to conduct the risk–benefit assessment and monitor the impact.

The above issues call for WHO to provide practical guidance to:

- countries on how they could move steadily towards introducing quality G6PD testing with currently available tools in all *P. vivax* patients before providing radical cure, while at the same time not compromising early *P. vivax* diagnosis and treatment programmes in settings where current G6PD tests cannot feasibly be deployed; and
- national malaria programmes on how to perform a risk–benefit analysis to inform decision-making on administering or withholding radical cure when a patient's G6PD status is unknown, assessing the prevalence and type of G6PD deficiency alleles prevalent in the country, testing for and interpreting G6PD tests, and managing the risk of haemolysis when primaquine is administered when G6PD status is not known.

The following are proposed:

- WHO recommendations made on preventing relapse in the current WHO *Guidelines for the treatment of malaria* (1) and in the *Control and elimination of Plasmodium vivax malaria – A technical brief* (2) remain unchanged.
- In translating these recommendations to action plans in countries, the following (or similar) guidelines be provided by WHO in (or as an addendum to) the *P. vivax* technical brief (2).

Where feasible, all patients with confirmed *P.vivax* and *P.ovale* should be tested for G6PD deficiency before administration of 14-day radical treatment with primaquine. There is limited experience in programmatic settings with currently available point-of-care, rapid diagnostic format tests for G6PD. Also, these tests may not be appropriate for use at the lower levels of the health system by health workers with limited skills and training, because the performance

of these tests is sensitive to temperature, the visual read out is more subjective than for malaria rapid diagnostic tests (RDTs) and there is a lack of integrated controls and quality control materials to allow for performance monitoring. Other potentially more robust point-of-care technologies have recently been commercialized but have not been independently assessed or achieved stringent regulatory approval; therefore, those technologies cannot be recommended for use. Hence, countries may use the following guiding principles as they move towards G6PD testing and implementing radical cure with primaquine for all confirmed *P. vivax* patients in the future:

- All countries in the phases of malaria elimination or in prevention of re-introduction (or both) should incorporate G6PD testing with currently available tests into treatment guidelines, and ensure that all *P. vivax* patients who do not know their G6PD status are tested before the administration of primaquine anti-relapse therapy.
    - In these phases of the programme, the patient load is extremely low, and, by requirement, patients are treated under close surveillance and often hospitalized. Thus, G6PD testing and administration of primaquine for radical cure should be entirely feasible.
- Countries where the prevalence of G6PD deficiency is known to be very low, and where G6PD testing is not currently considered mandatory on the basis that the potential benefits (related to the probability of relapse) exceed the risk of adverse consequences of primaquine treatment, should continue, while taking all precautions to educate the patient about the possible risk. Patient counselling should explicitly state that patients should stop the medicine and seek medical care if they become ill or their urine becomes red or black. The pharmacovigilance system need to be strengthened in these countries, to report on acute haemolytic anaemia induced by primaquine.
- Where both the burden of *P. vivax* malaria and the prevalence of G6PD deficiency is considerable, *P. vivax* patients should continue to be tested for malaria and treated for the blood-stage infection at all levels of the health system, particularly at the community level. A decision to administer primaquine anti-relapse therapy should be on one or both of the following:
    - individual patient assessment of the benefits of preventing relapse being assessed as exceeding the risk of giving primaquine (the risk depending on the population prevalence of G6PD deficiency, the severity of the prevalent genotypes, and the capacity of and accessibility to the health services that can identify and manage primaquine-induced haemolytic anaemia)
    - referring the patient to a higher level health facility for G6PD testing and primaquine treatment after providing treatment for the blood-stage infection.
- WHO should provide more specific guidance to countries on:
    - making risk–benefit assessments for radical cure;
    - assessing the feasibility of managing an acute haemolytic event when the G6PD status is unknown;
    - determining the population prevalence of G6PD and variants; and
    - G6PD testing of patients, where it is feasible, and interpretation of test results.

Such guidance may include an algorithm-based decision-making scheme, and defining factors that would enable effective management of haemolysis (e.g. distance to nearest hospital and blood bank, and a checklist for patient counselling and advice).

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2 WHO. Control and elimination of *Plasmodium vivax* malaria – A technical brief. Geneva, World Health Organization (WHO). 2015 (http://www.who.int/malaria/publications/atoz/9789241509244/en/, accessed 1 September 2015).

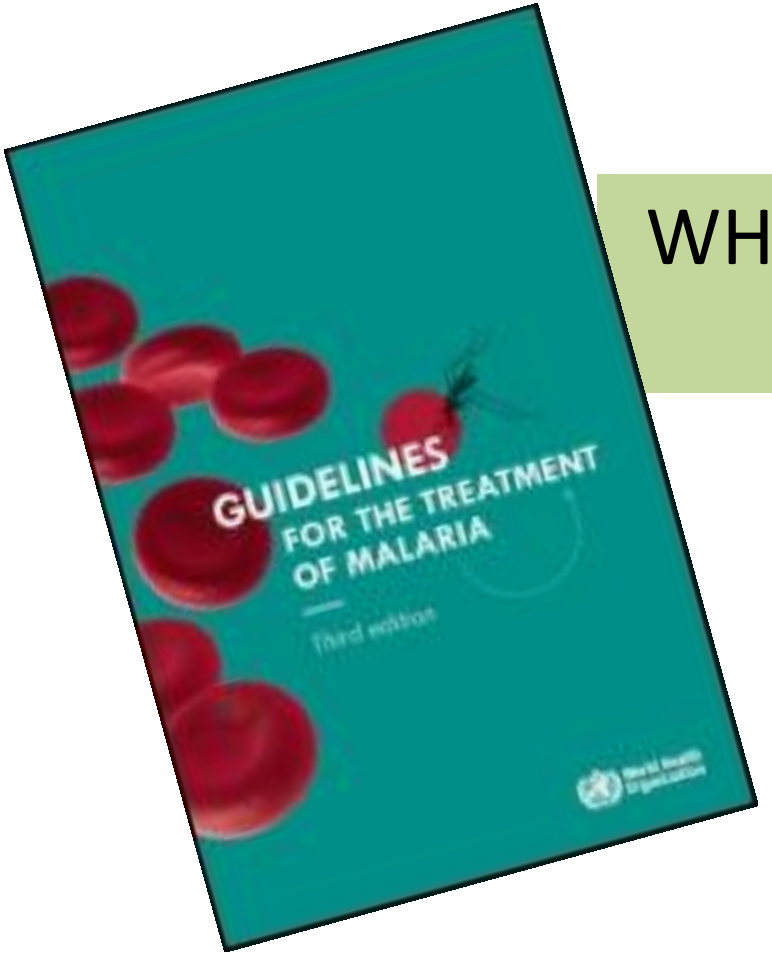
GLOBAL MALARIA PROGRAMME

World Health Organization

Implementation of G6PD testing and radical cure in *P. vivax* endemic countries: considerations

Malaria Policy Advisory Committee
Geneva, Switzerland
16-18 September 2015

WHO Guidelines on Radical Cure



WHO guidelines for the treatment of malaria 2015 (3rd ed)

WHO Guidelines on Radical Cure

Control and elimination of *Plasmodium vivax* malaria: A technical brief

Launched in WHO SEARO on 29 July 2015 at a Global Meeting in New Delhi attended by countries in all WHO Regions with endemic *P. vivax*

Discussions on translating guidelines into policy and strategy in programmes

WHO Guidelines on Radical Cure

- In both, recommendations are based on:
  - the need to radically cure patients using primaquine
  - minimizing the risk of primaquine-induced acute haemolysis in those who are deficient in the enzyme glucose-6-phospate dehydrogenase (G6PD)

WHO Guidelines

2.4.4 RECOMMENDATIONS

- Where feasible, all patients should be tested for G6PD deficiency before administering primaquine. Testing for G6PD deficiency in vivax malaria cases should be considered an integral part of ensuring universal access to diagnosis and treatment.
- G6PD testing should be incorporated into treatment guidelines, and services made available as tools are developed (possibly with referral of patients from lower to higher level health facilities).
- Where no G6PD test is available, it is difficult to generalize on the correct approach to patient management, because each individual assessment depends on the risk of adverse consequences (related to the likely dose of primaquine required, the prevalence and severity of G6PD deficiency in the area, the degree of anaemia and the availability of blood transfusion) and the potential benefits (related to the probability of relapse). In some circumstances, the assessment will favour withholding primaquine, and in others it will favour starting radical treatment after educating the patient about the possible risks, and informing the patient that they should stop the drug if they become ill or their urine becomes red or black.

Difficulties in Implementation Expressed by Countries

- The lack of a robust, easy-to-use point-of-care test for G6PD
  - makes it difficult to test at the lower levels of the health system.
  - Referral to higher levels is problematic, and may result in *P. vivax* patients not being treated.

- Some countries (eg, in the Americas) are already implementing radical cure at HF level without testing for G6PD
  - G6PD deficiency allele frequency is very low (and variants are mild) or absent. - benefits exceed the risks
  - Full compliance with recommendations could prevent expansion and reverse implentation

Countries Request Practical Guidance from WHO

- To move towards testing and radical cure when improved tools are available, & until then, not compromise the early treatment of *P. vivax* in settings where G6PD testing is currently not feasible.
- How to perform risk-benefit assessment when G6PD status is unknown on making a decision on administering or withholding radical cure

MPAC Advice to WHO

- Current WHO recommendations remain unchanged in both documents.
- In translating these recommendations to action plans in countries, the following (or similar) guidelines be provided by WHO in (or as an addendum to) the *P. vivax* technical brief.

MPAC Advice to WHO

- Where feasible, all patients with confirmed *P. vivax* and *P. ovale* should be tested for G6PD deficiency before administration of 14-day radical treatment with primaquine.
- Because current G6PD tests may not be appropriate for use at the lower levels of the health system, countries may use the following guiding principles:

MPAC Advice to WHO

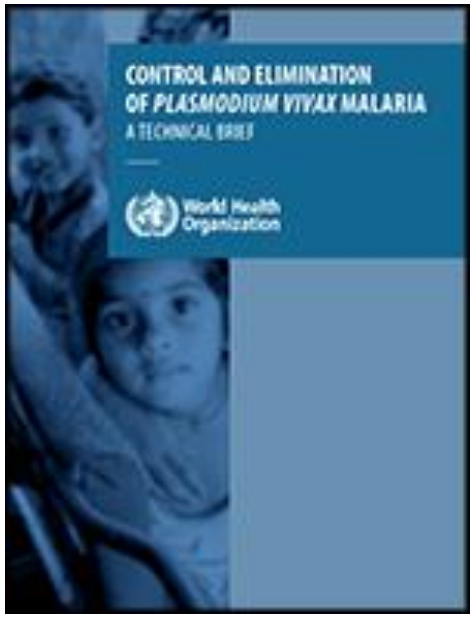
- All countries in the phases of malaria elimination and/or in prevention of re-introduction:
  - ensure that all *P. vivax* patients who do not know their G6PD status are tested before the administration of primaquine anti-relapse therapy.
- Countries where the prevalence of G6PD deficiency is known to be very low, and where G6PD testing is not currently considered mandatory:
  - should continue, while taking all precautions to educate the patient about the possible risk and strengthen their pharmacovigilance systems and the response arm.

MPAC Advice to WHO

- Where both the burden of *P. vivax* malaria and the prevalence of G6PD deficiency is considerable:
  - *P. vivax* patients should continue to **be tested for malaria and treated for the blood-stage infection at all levels of the health system, particularly at the community level.**
  - A decision to administer primaquine anti-relapse therapy should be on one or both of the following:
    - individual patient assessment of the risk/benefits
    - referring the patient to a higher level health facility for G6PD testing and primaquine treatment **after providing treatment for the blood-stage infection.**

MPAC Advice to WHO

- WHO should provide more specific guidance to countries on:
  - determining the population prevalence of G6PD and variants;
  - making risk–benefit assessments for radical cure;
  - assessing the feasibility of managing an acute haemolytic event when the G6PD status is unknown;
  - G6PD testing of patients, where it is feasible, and interpretation of test results.



On page 31….

"To achieve a radical cure (cure and prevention of relapse), a 14-day course of primaquine is recommended, after exclusion of G6PD deficiency….”

When can malaria control and elimination programs safely reduce vector control efforts? a simulation study.

Joshua Yukich and Nakul Chitnis

31 July 2015

Abstract

We use a simulation model of malaria epidemiology and immunology (OpenMalaria) to predict malaria transmission and disease outcomes after withdrawing vector control interventions under various settings. We analyze simulation results using logistic and linear regression in order to derive predicted probabilities of resurgence and predictions of severity of resurgence under scenarios defined by the baseline pre-intervention entomological inoculation rate (EIR), case management coverage, and vector control coverage, amongst other parameters. We also use Monte Carlo simulations to examine the precision and bias associated with metrics estimated by control programs to determine if a setting meets the criteria for the safe reduction in coverage of vector control interventions. Results indicate that, in the absence of secular changes in the underlying determinants of transmission (historically called receptivity), there are few scenarios under which vector control can be removed without a strong expectation of resurgence. These, potentially safe, scenarios are characterized by low historic EIR, successful control with vector control reaching elimination or near elimination, and effective surveillance systems with high coverage and effective treatment of malaria cases.

1 Background

The World Health Organization (WHO) Global Malaria Programme's (GMP) policy of universal coverage of long lasting insecticidal nets (LLINs) and/or indoor residual spraying (IRS) of people living in areas of malaria transmission, implemented as one of the fundamental components of malaria control and elimination strategies, and following the issuance of the Global Malaria Action Plan (GMAP) [1, 2], with funding from the Global Fund for HIV/AIDS, Tuberculosis and Malaria (GFATM), United States Agency for International Development (USAID) President's Malaria Initiative (PMI) and others, has led to large increases in global coverage of vector control for malaria and concomitant declines in malaria burden and transmission in many parts of the world [1]. This scale up, however, is not without cost and many national malaria control programs wonder if it is possible, after successful vector control has been achieved and burden reductions realized to scale down from universally applied vector control measures to more focal approaches, and if transmission and burden reductions could be maintained, even in the absence of vector control.

This document outlines the broad questions that need to be answered in order for the WHO to provide guidance on when or if such a reduction in vector control coverage might be possible for a specific place and time to transition from a target of universal coverage to either complete cessation of vector control activities or to lower or more focal coverage based on local data. We note here that the scale back of vector control interventions may be implemented at small sub-national scales and not only at the country level. The need for such guidance was further emphasized in country consultations during the development of the Global Technical Strategy.

Some points should be considered at the outset. Firstly, in historical examples, including many countries or areas which have achieved WHO certified malaria elimination, vector control may still be practiced and/or often remains a part of a response strategy to introduced malaria cases (often focally around the

cases). Secondly, even in countries with a long history of certified malaria elimination and an absence of demonstrated autochthonous transmission, malaria transmission potential may remain indefinitely [3] — as recent outbreaks of autochthonous transmission in Greece, the United States, the Bahamas, Singapore and other locations demonstrate [4, 5, 6, 7].

2 Questions

Four questions need to be answered to ensure that any guidance on scaling back from universal vector control coverage is accurate and safe. These are as follows:

1. In a place with historical malaria transmission and high coverage of vector control interventions, are there situations in which reduction in the level of effort or coverage of vector control activities will *not* result in resurgent transmission and accompanying increases in disease burden?
2. What set of indicators would be necessary to specifically identify locations and times in which the scaling back of vector control might be safely undertaken as per the conditions set above in Question 1?
3. What is the impact of the precision and bias associated with these measurements on estimates of the risk of resurgence following the scale back of vector control?
4. What sets of measurements of these indicators would indicate that vector control could be safely scaled back?

3 Methods

3.1 Outline

OpenMalaria is a simulation platform, consisting of an ensemble of models of malaria epidemiology and immunology, that allows the comparison of the effectiveness and cost-effectiveness of current and planned control interventions in various settings [8]. We run simulations of these models to determine the effects of scaling back from universal coverage of vector control interventions, specifically long lasting insecticidal nets (LLINs). We run simulations with multiple random seeds to include the effects of stochasticity; different model versions to include uncertainty in underlying model assumptions; and multiple parameterizations to allow for various assumptions of base (pre-intervention) transmission level, coverage of indoor vector control interventions, rate of imported infections, and coverage of case management and mass treatment interventions. The outputs of the simulations include the number of episodes of uncomplicated malaria, and the probability of resurgence following the scaling back of vector control.

3.2 Overview of Model

The OpenMalaria model platform combines an ensemble of stochastic individual-based model for malaria in humans with a periodically-forced deterministic model for malaria in mosquitoes, shown in a simple schematic in Figure 1. The model uses a discrete time step of five days and includes multiple aspects of the dynamics of malaria in humans, including demography; acquired immunity and superinfection; variations in parasite densities and infectiousness to mosquitoes; and the clinical effects of malaria and has been fit to multiple field data sets [9]. The model for malaria transmission in mosquitoes includes multiple mosquito species, nonhuman hosts, and a periodically varying emergence rate [10]. We show a schematic of the female mosquito's feeding cycle and the effects of vector control interventions in Figure 2. We have used this model platform to investigate the effects of vector control interventions, vaccines, chemoprophylaxis and case management in reducing malaria transmission and disease.

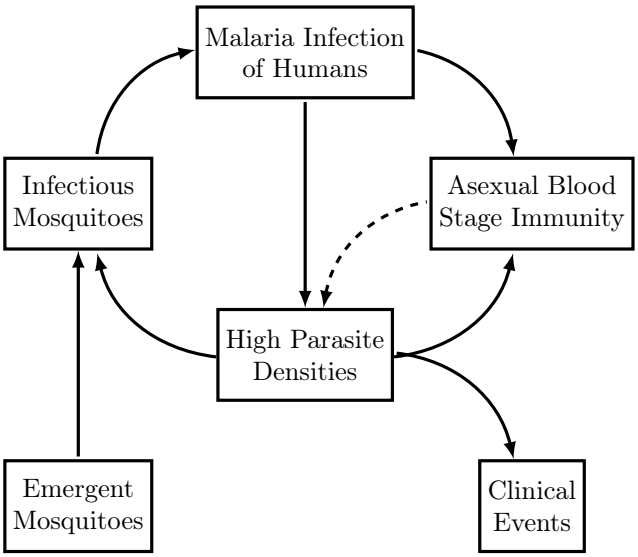


Figure 1: Schematic of the malaria transmission model with positive feedback shown by solid lines and negative feedback by dashed lines. Emergent mosquitoes biting on humans with high parasite densities are more likely to become infected and subsequently infectious if they live long enough. They, in turn, can infect humans, leading to high parasite densities and the build up of acquired immunity. Acquired immunity tends to moderate parasite densities, which can lead to clinical events, such as uncomplicated malaria, severe malaria, and death.

3.3 Model Simulations and Sensitivity Analysis

We create baseline parameterizations that describe pre-intervention transmission in western Kenya and the Solomon Islands(including the composition of mosquito vectors and the seasonal profile of transmission). We run numerical simulations for a population of 10,000 humans of this baseline scenario and of simulations with different coverage levels of vector control and active case detection interventions and varying levels of pre-intervention transmission, imported infections, and case management coverage.

We run the model for one human life span where humans are subjected to a periodically varying pre-intervention entomological inoculation rate (EIR) to induce malaria immunity population and to estimate the mosquito emergence rate that leads to this EIR. After this warm-up period and a short stabilizing period, we deploy LLINs to humans through four mass distribution campaigns repeated every three years. Coinciding with the last deployment of nets, we conduct quarterly mass screen and treat campaigns to simulate active case detection in the population for the remainder of the simulation. A schematic of the generic simulation scenario is shown in Figure 3.

We survey the population for a total of thirty-two years, measuring the annual EIR, the number of new infections, the number of patent infections, the number of uncomplicated clinical malaria cases per person per year, and the number of diagnostic tests used, amongst other parameters. We monitor the first three years as the baseline period in the absence of any interventions (but with ongoing case management of clinical cases). We monitor the following nine years as the vector control period (between the first and the fourth deployment of LLINs) and additionally determine the probability of elimination within this period. We monitor the final twenty years as the post-vector control period and additionally determine the probability of resurgence within this period. We note that the post-vector control period begins directly after the final distribution of LLINs so a proportion of the population will be initially protected by effective LLINs.

Since the simulations stochastically include imported infections, complete cessation of all transmission is

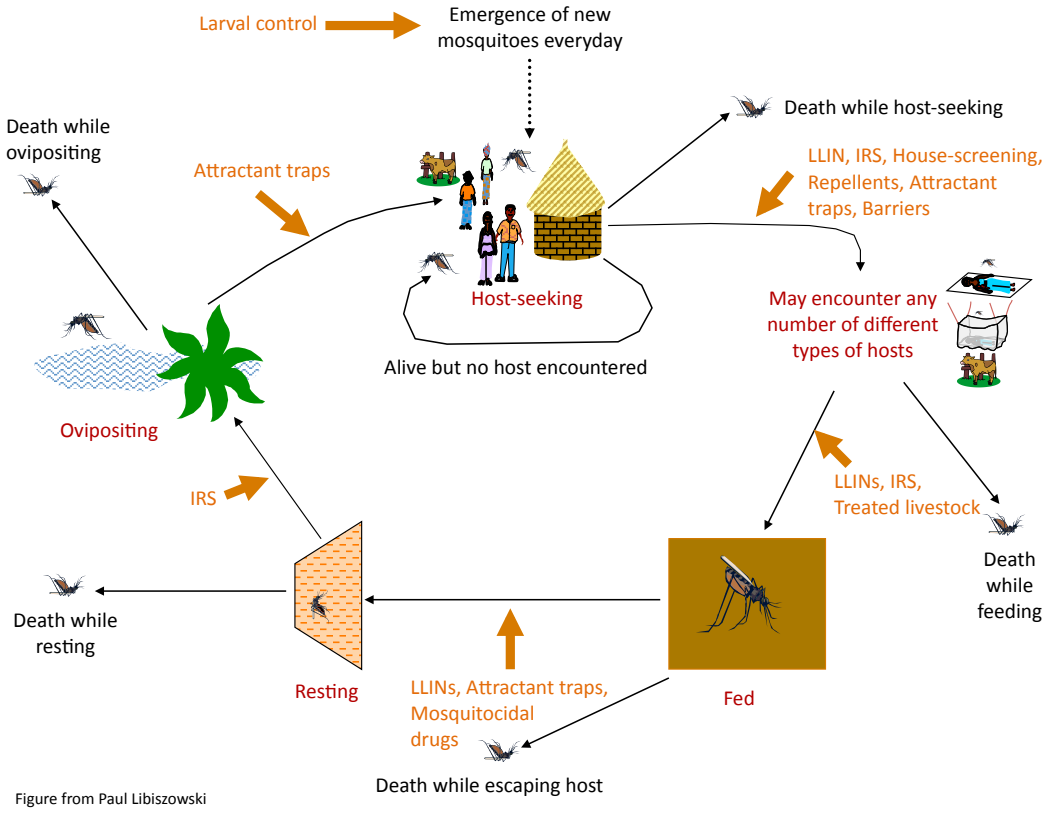


Figure 2: Schematic of mosquito feeding cycle dynamics including the effects of interventions.

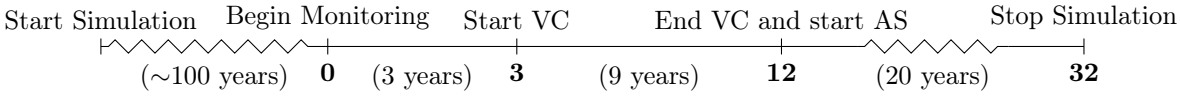


Figure 3: Schematic of generic scenario description for OpenMalaria simulations conducted for this study. "VC" stands for vector control and "AS" stands for active surveillance. Bold numbers indicate reference years for monitoring.

unlikely. Therefore, we define elimination during the vector control period as occurring when the number of new infections on one year is less than 3 times the 97.5 percentile of the Poisson distribution of the number of imported infections (in one year), as defined in a previous publication [11]. Similarly, we define resurgence in the post-vector control period as occurring when the number of new infections in one year is greater 3 times the 97.5 percentile of the Poisson distribution of the number of imported infections (in one year).

3.3.1 Baseline Western Kenya Parameterization

We use previously published work [12] to form the baseline transmission parameterization for western Kenya, and the parameterization of the initial effectiveness of nets and their rate of decay.

3.3.2 Baseline Solomon Islands Parameterization

For the baseline transmission in Solomon Islands, we use United Nations population data [13] to estimate the human demographic profile. The main vector species in the Solomon Islands is *Anopheles farauti*. We use a seasonality profile for the EIR calculated from climate data by the EMOD model [14]. We determine the extrinsic incubation period and the duration of the mosquito resting phase from average temperature data in Guadalcanal. We use data for *An. farauti* from Papua New Guinea for the human blood index [15] and for the probability of mosquitoes host seeking the same day as oviposition [16]. We use data from northern Guadalcanal for the parous proportion of mosquitoes and the proportion of mosquitoes that biting indoors at the time when humans are sleeping indoors [17]. Other parameters such as the treatment drugs, decay and effectiveness of LLINs and sensitivity of rapid diagnostic tests are assumed to be similar to Kenya.

3.3.3 Experiment Set-up

To conduct a more thorough sensitivity analysis, we vary:

Transmission level: we consider levels of baseline (pre-intervention) EIR of $\{0.1, 0.5, 1, 2, 5\}$ infectious bites per adult per year to represent historical transmission;

Coverage of vector control interventions: we vary coverage of LLINs of $\{0, 0.2, 0.5, 0.8\}$;

Importation rate: we model importation rates of $\{0.1, 1, 10\}$ infections per 1000 people per year;

Case management coverage: we assume case management coverage of $\{0.2, 0.5, 0.8\}$ of all uncomplicated cases that are treated effectively;

Active case detection: we simulate mass screen and treat interventions every 3 months at coverage levels of $\{0, 0.025, 0.1, 0.2\}$ to model increased active surveillance;

Stochasticity: we use 10 random seeds per model parameterization;

Model variants: we use 14 model variants as described in a previous publication [18] to explore the implications of various model assumptions such as possible decay of immunity and correlation of heterogeneities.

3.4 Precision and Bias

In order to examine the potential for real surveillance systems to mis-measure or misclassify important metrics suggested here as tools for determining the safety of vector control withdrawal we have conducted several additional simulation exercises using Monte Carlo Simulation algorithms developed using R software [19] to estimate the precision and bias inherent in measurements of the infection importation rate (IIR) and the annual blood examination rate (ABER).

3.4.1 Infection Importation Rate

In order to estimate the precision and bias associated with measurement of IIR we conducted simulations of importation and measurement assuming that the number of importations weekly was given by a Poisson distribution with a mean of the true IIR, we then assumed that there was a observation process given by a binomial distribution which determined whether each of the imported infections was actually detected. We simulated this process for a one year period (52 weeks) and repeated the simulations for 10,000 iterations assuming varied mean true IIRs (from 1 per 1,000 persons per annum to 5 per 1,000 persons per annum) and varied detection rates (from 20% to 80%). We then tested each result against a threshold of 2 per 1,000 per annum to determine if, for each simulation, a Poisson significance test would determine that the number of imported infections per year would be determined to be statistically significantly below the threshold with $\geqslant 90\%$ confidence. This sequence of results were then analyzed with logistic regression and the predicted probability of concluding that IIR (based on the measurement) was below the threshold was summarized by true IIR and the detection probability in the surveillance system.

3.4.2 Annual Blood Examination Rate

In order to estimate the potential bias associated with utilizing ABER as a metric for surveillance system coverage we conducted simulations designed to determine the divergence between ABER and the total proportion of a population tested during one year with multiple active case searches covering varying proportions of the population where individuals have varied probabilities to be covered: in other words, where the active searches are likely to repeatedly test or miss the same individuals. We simulated a cohort of individuals with either independent probabilities of being tested in each round, equal to the total proportion covered during said round, or by assuming that all individuals in the cohort had a constant predetermined probability of inclusion during all rounds. These probabilities were generated by simulating from a beta distribution with a known mean. The actual inclusion of an individual as tested in a round was drawn from a binomial distribution with probability determined in one of the two above methods. The annual blood examination rate was calculated as,

$$\text{ABER} = \frac{\text{Number of Tests Conducted}}{\text{Person-Years}}, \tag{1}$$

while the the proportion of the population actually tested was calculated as,

$$\text{PT} = \frac{\text{Number of Individuals Tested}}{\text{Person-Years}}. \tag{2}$$

4 Results

4.1 Precision and Bias

The predicted probabilities from the logistic model for decisions based on IIR are shown in Figure 4. These results indicate that as the surveillance system improves (increases the probability of detecting imported infections) that there is relatively little chance of incorrectly concluding that the importation rate is below a specified threshold in error. However, the results also show that when the surveillance system has a high probability of detecting imported infections, programs will often not be able to conclude that the IIR is low enough to withdraw vector control unless the true IIR is significantly below the acceptable threshold of risk.

The results of simulation of ABER are shown in Figure 5. They indicate that although ABER and the proportion of the population actually tested by a surveillance system are likely to greatly diverge at high values, at the lower levels of interest here, they are likely to be largely similar. Thus at least at lower levels of testing, ABER is likely to be a reliable metric for the monitoring surveillance system coverage.

Results of an analysis of OpenMalaria simulation outputs indicates a further complication in monitoring and determining whether an area meets the acceptability threshold for withdraw of vector control, which is that the annual parasite index (API) and ABER are both highly correlated in these individual simulation

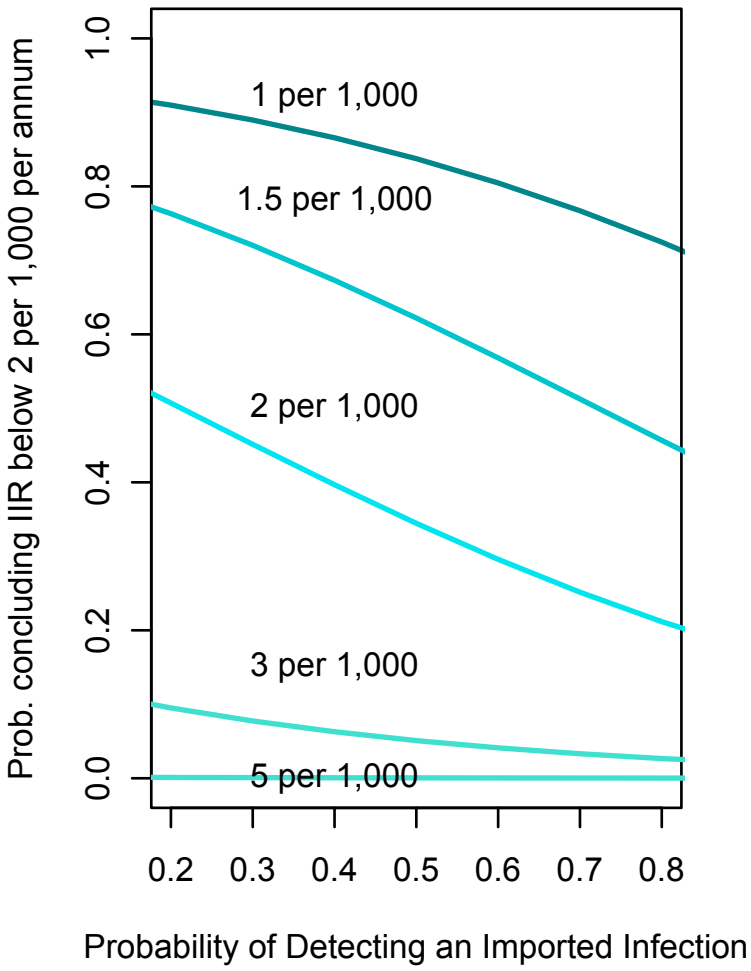


Figure 4: Simulation Results for Measurement of Infection Importation Rate

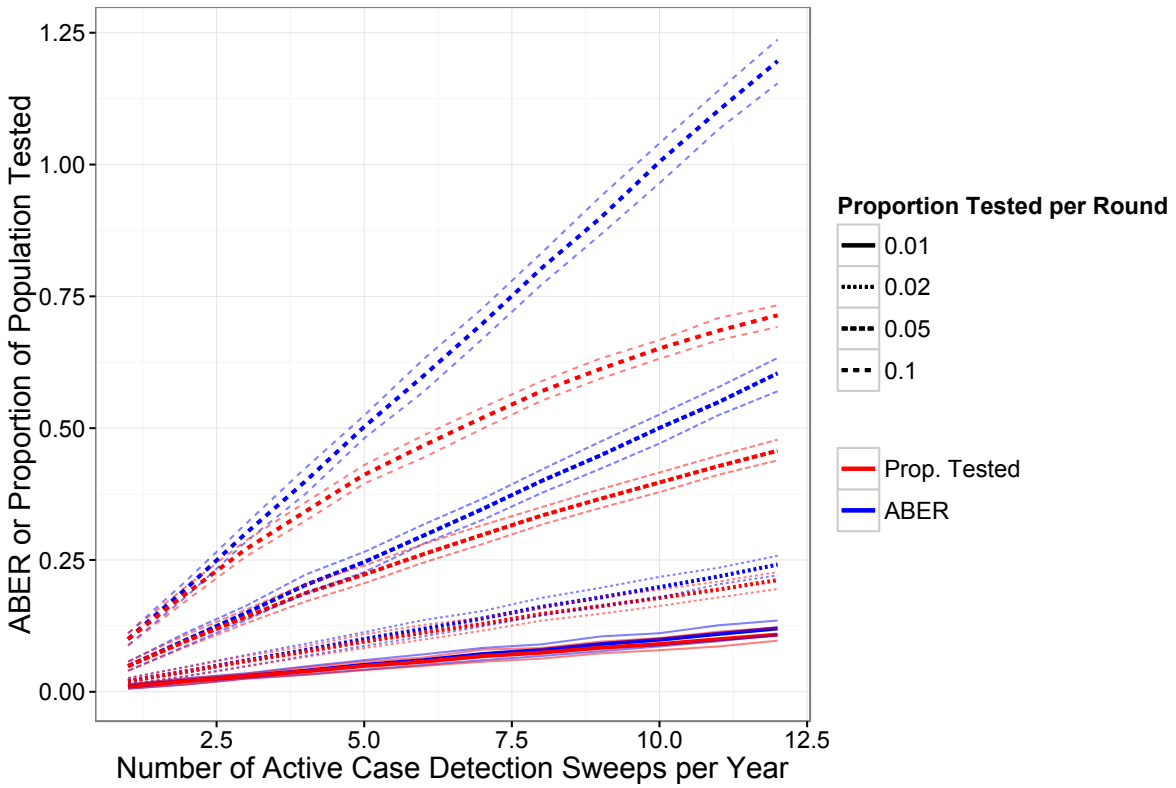


Figure 5: Simulation Results for Measurement of the Annual Blood Examination Rate.

outputs. This is likely because API is essentially a product of the positivity rate among those tested and ABER, therefore, API tends to increase with increases in ABER. We elaborate on this point further in the discussion.

4.2 Descriptive results of OpenMalaria simulation outputs: Kenyan Context

Simulation outputs allowed for the calculation of the time course of API, ABER and the incidence of new malaria infections (or force of infection (FOI)). The results of some sample simulations are shown in Figure 6. Results of a subset of simulations for ABER are shown in Figure 7. API provides a metric for estimation of true infection incidence, especially at high case management coverage and low EIR. However, because this metric can be biased by health system access (case management coverage) and active surveillance activities, we do not use it to define the occurrence of a resurgence of malaria or as a metric for determining that vector control has successfully interrupted transmission or reduced it to any significant extent. We instead use the number of new infections (including super infections) at each model time step. This metric is similar to a molecular force of infection (mFOI) measure, and also to standard FOI measures at low transmission where super-infection is expected to be rare. Figure 8 shows the results of simulations of this metric for a subset of relevant simulation outputs.

We determined for each simulation run, if transmission had effectively been interrupted by vector control and whether or not there was a resurgence of transmission following the withdrawal of vector control. Descriptive results are shown in Tables 1–6 for elimination and resurgence by various input parameters. Most simulations resulted in elimination during vector control roll-out. However, a similar fraction of simulations

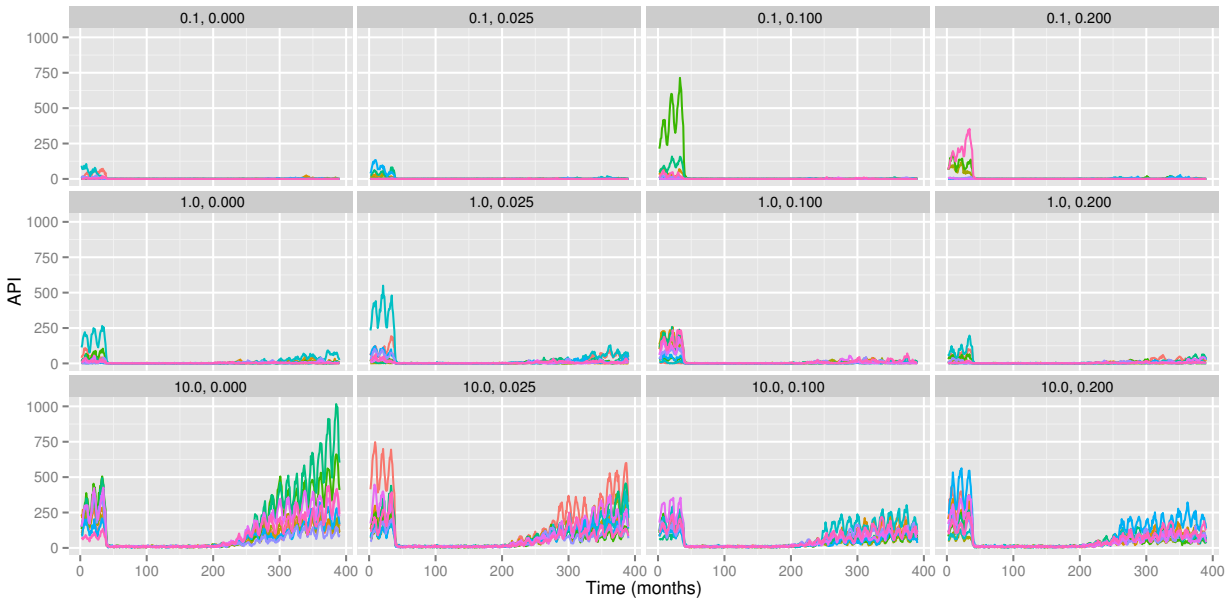


Figure 6: OpenMalaria simulation results for API per 1,000 per annum (Kenya scenario) with an annual pre-intervention EIR of 0.1, case management coverage of 80%, and LLIN coverage of 80% during the period of vector control implementation. Each chart shows simulations results for varied levels of the infection importations rate and active surveillance (through quarterly mass screening and treatment (MSAT) coverage). These values are shown just above each chart in the form (IIR per thousand per year, proportion of population tested per quarter). Colors of lines within the chart represent various simulation runs with differing random seeds (thus capturing stochastic uncertainty). API is the annual parasite incidence computed at each time step and the x-axis is in months. LLINs are distributed at months 36, 72, 108, 144. Increased active surveillance starts immediately coincident with the last distribution of vector control.

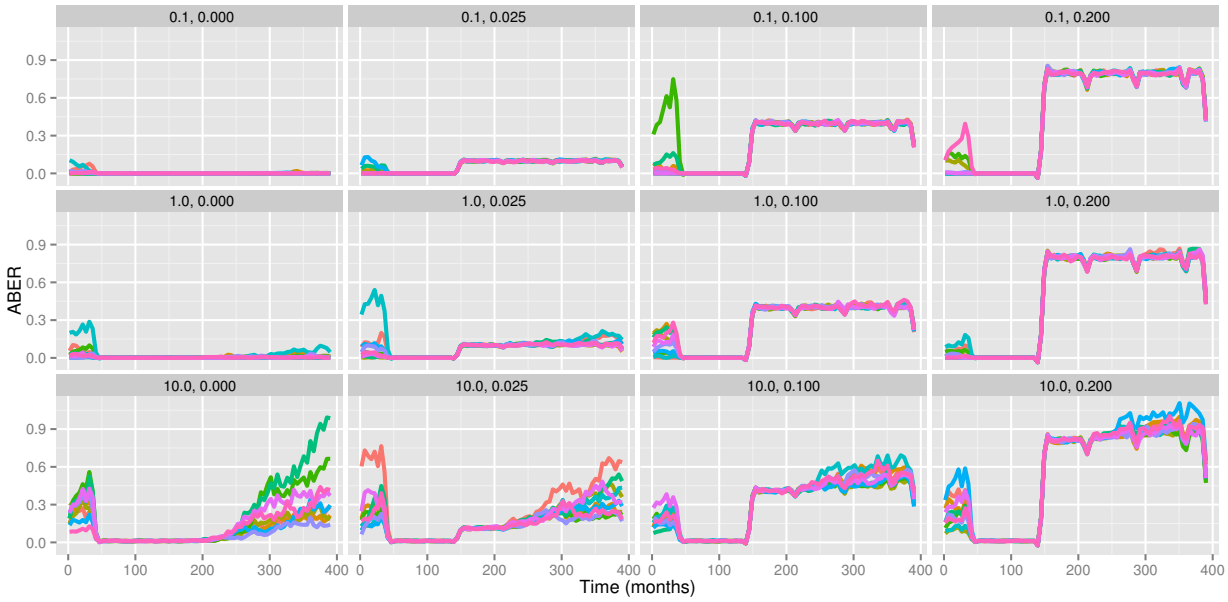


Figure 7: OpenMalaria simulation results for ABER (Kenya scenario) with an annual pre-intervention EIR of 0.1, case management coverage of 80%, and LLIN coverage of 80% during the period of vector control implementation. Each chart shows simulations results for varied levels of the infection importations rate and active surveillance (through quarterly mass screening and treatment (MSAT) coverage). These values are shown just above each chart in the form (IIR per thousand per year, proportion of population tested per quarter). Colors of lines within the chart represent various simulation runs with differing random seeds (thus capturing stochastic uncertainty). ABER is the annual blood examination rate (smoothed to remove the visual effects of widely varying ABER between time periods with quarterly MSAT surveys) and the x-axis is in months. LLINs are distributed at months 36, 72, 108, 144. Increased active surveillance starts immediately coincident with the last distribution of vector control.

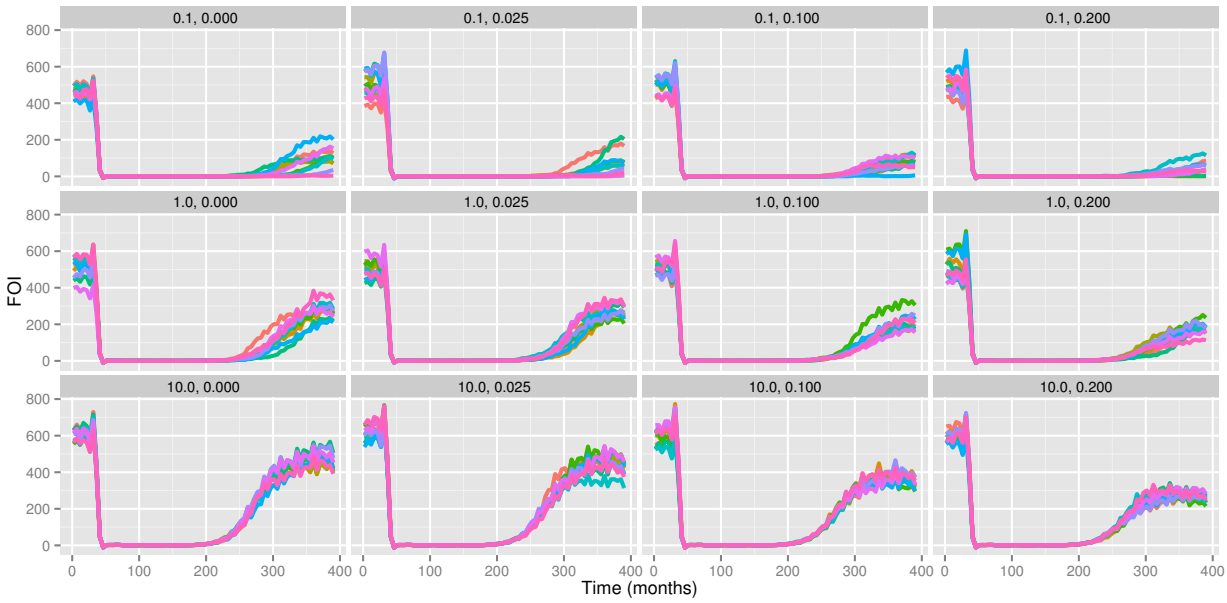


Figure 8: OpenMalaria simulation results for mFOI per 1,000 per annum (Kenya scenario) with an annual pre-intervention EIR of 1, case management coverage of 80%, and LLIN coverage of 80% during the period of vector control implementation. Each chart shows simulations results for varied levels of the infection importations rate and active surveillance (through quarterly mass screening and treatment (MSAT) coverage). These values are shown just above each chart in the form (IIR per thousand per year, proportion of population tested per quarter). Colors of lines within the chart represent various simulation runs with differing random seeds (thus capturing stochastic uncertainty). mFOI is the molecular force of infection per 1,000 people per year and the x-axis is in months. LLINs are distributed at months 36, 72, 108, 144. Increased active surveillance starts immediately coincident with the last distribution of vector control.

showed resurgence after vector control withdrawal (Table 1). When results for resurgence and elimination were examined in bivariate analysis for background characteristics of simulation, occurrence of a resurgence was statistically significantly associated with infection importation rate, case management coverage, active surveillance coverage, input EIR, model variant and the level of vector control coverage achieved (Tables 2–7). While elimination was associated with level of vector control coverage achieved, case management coverage, input EIR and model variant (Tables 2 and 7).

Overall, there were 99,977 successfully completed simulations (a small number of simulation runs (23) failed to complete). In the majority of simulations (69%) the level of malaria transmission during vector control deployment met the criteria for elimination during vector control deployment. The majority of simulations (55%) also resulted in a resurgence after vector control withdraw (Table 1). Table 1 shows the proportion of simulations which resulted in elimination and resurgence.

Variable	**Levels**	$\mathbf{n}_0$	$\%_0$	$\mathbf{n}_1$	$\%_1$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	30978	100.0	0	0.0	30978	31.0
	1	0	0.0	68999	100.0	68999	69.0
$p < 0.0001$	all	30978	100.0	68999	100.0	99977	100.0
Resurgence	0	1519	4.9	43923	63.7	45442	45.5
	1	29459	95.1	25076	36.3	54535	54.5
$p < 0.0001$	all	30978	100.0	68999	100.0	99977	100.0

Table 1: Simulation outputs for elimination and resurgence

Increasing coverage of ITNs during vector control deployment was associated with increased probabilities of elimination and as well as reduced probabilities of resurgence (Table 2).

Variable	**Levels**	$\mathbf{n}_0$	$\%_0$	$\mathbf{n}_{0.2}$	$\%_{0.2}$	$\mathbf{n}_{0.5}$	$\%_{0.5}$	$\mathbf{n}_{0.8}$	$\%_{0.8}$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	23530	94.2	7342	29.4	106	0.4	0	0.0	30978	31.0
	1	1456	5.8	17642	70.6	24915	99.6	24986	100.0	68999	69.0
$p < 0.0001$	all	24986	100.0	24984	100.0	25021	100.0	24986	100.0	99977	100.0
Resurgence	0	1728	6.9	11683	46.8	15275	61.0	16756	67.1	45442	45.5
	1	23258	93.1	13301	53.2	9746	39.0	8230	32.9	54535	54.5
$p < 0.0001$	all	24986	100.0	24984	100.0	25021	100.0	24986	100.0	99977	100.0

Table 2: Simulation outputs for elimination and resurgence in terms of ITN coverage during vector control

Changes in active surveillance across the range tested was not statistically significantly related to the probability of elimination. Increasing active surveillance coverage was significantly associated with a downward trend in the probability of resurgence. Since active surveillance was not deployed during the period of vector control in these simulations the lack of any association with elimination during vector control is expected (Table 3).

Variable	**Levels**	$\mathbf{n}_0$	$\%_0$	$\mathbf{n}_{0.025}$	$\%_{0.025}$	$\mathbf{n}_{0.1}$	$\%_{0.1}$	$\mathbf{n}_{0.2}$	$\%_{0.2}$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	7804	31.0	7558	31.0	7830	31.1	7786	30.9	30978	31.0
	1	17389	69.0	16837	69.0	17367	68.9	17406	69.1	68999	69.0
$p = 0.98$	all	25193	100.0	24395	100.0	25197	100.0	25192	100.0	99977	100.0
Resurgence	0	10499	41.7	10442	42.8	11672	46.3	12829	50.9	45442	45.5
	1	14694	58.3	13953	57.2	13525	53.7	12363	49.1	54535	54.5
$p < 0.0001$	all	25193	100.0	24395	100.0	25197	100.0	25192	100.0	99977	100.0

Table 3: Simulation outputs for elimination and resurgence in terms of active surveillance coverage

Changes in the level of case management coverage were associated with differences in the probability of elimination and resurgence (Table 4).

Variable	**Levels**	$\mathbf{n}_{0.2}$	$\%_{0.2}$	$\mathbf{n}_{0.5}$	$\%_{0.5}$	$\mathbf{n}_{0.8}$	$\%_{0.8}$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	11439	34.0	10015	30.5	9524	28.4	30978	31.0
	1	22161	66.0	22781	69.5	24057	71.6	68999	69.0
$p < 0.0001$	all	33600	100.0	32796	100.0	33581	100.0	99977	100.0
Resurgence	0	11646	34.7	15419	47.0	18377	54.7	45442	45.5
	1	21954	65.3	17377	53.0	15204	45.3	54535	54.5
$p < 0.0001$	all	33600	100.0	32796	100.0	33581	100.0	99977	100.0

Table 4: Simulation outputs for elimination and resurgence in terms of case management coverage

Input entomological inoculation rate (EIR) was strongly associated with probabilities of both elimination and resurgence. These associations showed trends in the expected directions with elimination much less likely to occur at higher input EIRs and resurgence much more likely to occur at higher baseline EIRs (Table 5).

Variable	**Levels**	$\mathbf{n}_{0.1}$	$\%_{0.1}$	$\mathbf{n}_{0.5}$	$\%_{0.5}$	$\mathbf{n}_1$	$\%_1$	$\mathbf{n}_2$	$\%_2$	$\mathbf{n}_5$	$\%_5$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	3753	18.8	4845	24.2	5206	26.0	7151	35.8	10023	50.1	30978	31.0
	1	16224	81.2	15155	75.8	14794	74.0	12849	64.2	9977	49.9	68999	69.0
$p < 0.0001$	all	19977	100.0	20000	100.0	20000	100.0	20000	100.0	20000	100.0	99977	100.0
Resurgence	0	15531	77.7	12172	60.9	9313	46.6	6348	31.7	2078	10.4	45442	45.5
	1	4446	22.3	7828	39.1	10687	53.4	13652	68.3	17922	89.6	54535	54.5
$p < 0.0001$	all	19977	100.0	20000	100.0	20000	100.0	20000	100.0	20000	100.0	99977	100.0

Table 5: Simulation outputs for elimination and resurgence in terms of input entomological inocculation rate

Infection Importation Rate (IIR) was significantly associated with the probability of resurgence but not with elimination (Table 6).

Variable	**Levels**	$\mathbf{n}_{0.1}$	$\%_{0.1}$	$\mathbf{n}_{1}$	$\%_{1}$	$\mathbf{n}_{10}$	$\%_{10}$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	10370	31.1	10428	31.3	10180	30.5	30978	31.0
	1	22939	68.9	22887	68.7	23173	69.5	68999	69.0
$p = 0.07$	all	33309	100.0	33315	100.0	33353	100.0	99977	100.0
Resurgence	0	20920	62.8	14157	42.5	10365	31.1	45442	45.5
	1	12389	37.2	19158	57.5	22988	68.9	54535	54.5
$p < 0.0001$	all	33309	100.0	33315	100.0	33353	100.0	99977	100.0

Table 6: Simulation outputs for elimination and resurgence in terms of infection importation rate per 1,000 per annum

Model variant was also significantly associated with the probability of resurgence and elimination (Table 7).

Variable	Levels	n_{R0063}	$\%_{R0063}$	n_{R0065}	$\%_{R0065}$	n_{R0068}	$\%_{R0068}$	n_{R0111}	$\%_{R0111}$	n_{R0115}	$\%_{R0115}$	n_{R0121}	$\%_{R0121}$	n_{R0125}	$\%_{R0125}$	n_{R0131}	$\%_{R0131}$	n_{R0132}	$\%_{R0132}$	n_{R0133}	$\%_{R0133}$	n_{R0670}	$\%_{R0670}$	n_{R0674}	$\%_{R0674}$	n_{R0678}	$\%_{R0678}$	n_{base}	$\%_{base}$	n_{all}	$\%_{all}$
Elimination	0	2421	34.0	2197	30.8	2202	30.8	2253	31.6	2088	29.2	2229	31.2	2064	28.9	2167	30.3	2131	29.9	2143	30.0	2191	30.7	2319	32.5	2323	32.5	2250	31.5	30978	31.0
	1	4707	66.0	4942	69.2	4941	69.2	4887	68.5	5057	70.8	4916	68.8	5076	71.1	4978	69.7	5009	70.2	4997	70.0	4954	69.3	4825	67.5	4817	67.5	4893	68.5	68999	69.0
$p < 0.0001$	all	7128	100.0	7139	100.0	7143	100.0	7140	100.0	7145	100.0	7145	100.0	7140	100.0	7145	100.0	7140	100.0	7140	100.0	7145	100.0	7144	100.0	7140	100.0	7143	100.0	99977	100.0
Resurgence	0	3373	47.3	3831	53.7	3504	49.1	3418	47.9	3687	51.6	3314	46.4	3147	44.1	3156	44.2	2915	40.8	3203	44.9	3300	46.2	2691	37.7	2552	35.7	3351	46.9	45442	45.5
	1	3755	52.7	3308	46.3	3639	50.9	3722	52.1	3458	48.4	3831	53.6	3993	55.9	3989	55.8	4225	59.2	3937	55.1	3845	53.8	4453	62.3	4588	64.3	3792	53.1	54535	54.5
$p < 0.0001$	all	7128	100.0	7139	100.0	7143	100.0	7140	100.0	7145	100.0	7145	100.0	7140	100.0	7145	100.0	7140	100.0	7140	100.0	7145	100.0	7144	100.0	7140	100.0	7143	100.0	99977	100.0

Table 7: Simulation outputs for elimination and resurgence in terms of Model Variant (Kenya Vector Parametrization). Details of the models variants are provided in [18].

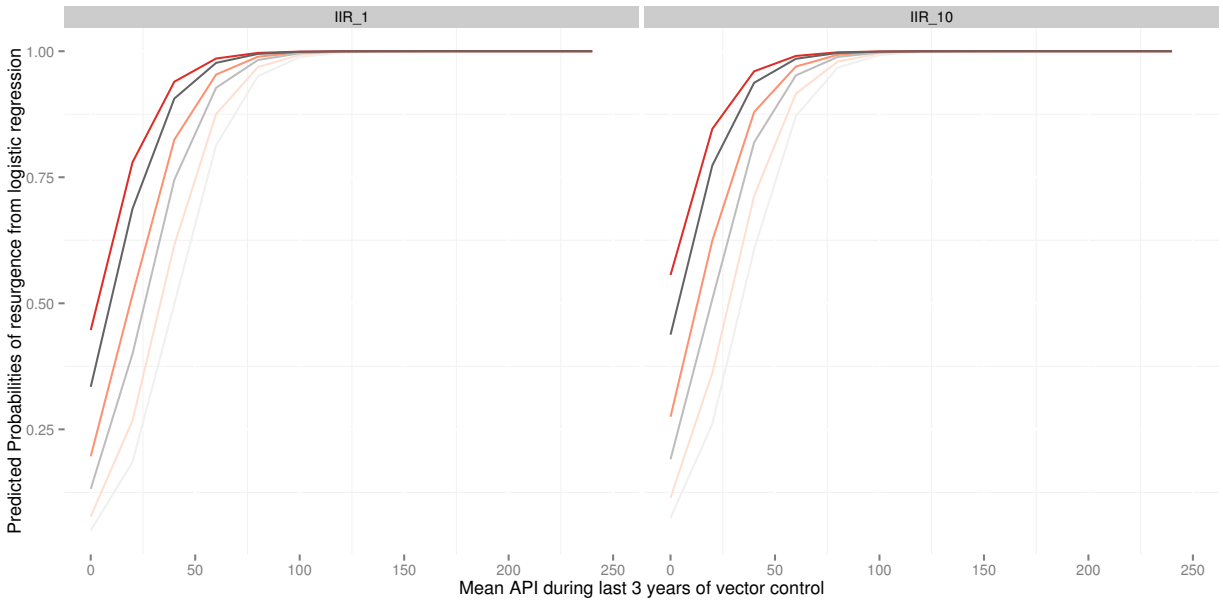


Figure 9: Predicted probabilities of resurgence based on regression results in Table 8. Darker lines represent increasing EIR (0.1, 1, 2), while grey lines represent Active surveillance coverage of 1% per quarter and red lines represent Active surveillance coverage of 10% per quarter. All slopes here are for ITN coverage of 80%, case management coverage of 50% and using the base model variant.

4.3 Regression results: Kenya

In order to estimate the impact of various predictors on the probability of resurgence and severity of resurgence following scale back of vector control in a multivariate framework, we applied logistic and linear regression using the input parameters, and malaria outcomes during vector control, of each simulation as predictors and the occurrence post-withdrawal as the outcome. The results are summarized in Table 8.

These results indicate that most parameters which were significant in bivariate analysis retained important predictive vale for the probability of a resurgence in multivariate analysis. Overall model results reinforce the importance of pre-intervention EIR, case management coverage, active surveillance coverage, infection importation and the level of control success during vector control deployment as major driving factors in predicting the probability of resurgence after withdrawal.

These logistic regression model results can be used to summarize the predicted probability of a resurgence occurring with varying levels of input parameters. Figure 9 shows the predicted probability of resurgence at varying levels of API, IIR, EIR and active surveillance coverage for the base model variant.

The predicted probability of resurgence is generally high for most parameter combinations and only falls below 0.25 for a set of simulations in which pre-intervention EIR was less than 1, IIR was 1 per 1,000 per year, mean API during vector control deployment was below 25 per 1,000 persons per year and there was some level of active surveillance. While the definition of a safe probability of resurgence would need to be defined for each particular setting, it is unlikely that a probability of resurgence greater than 0.25 would fall under this definition.

In order to estimate the effects of the various parameters on the severity of resurgence following vector control withdrawal we also used the proxy,

$$\text{Mean API}_{\text{After VC WD}} - \text{Mean API}_{\text{End VC}},$$

for the linear regression. Table 9 shows the results of this regression analysis.

Table 8: Logistic regression of input model parameters on resurgence

	Dependent variable:
	Resurgence
Mean API During VC (per 1000)	1.077***
	(1.072, 1.082)
Case Management Cov.	0.021***
	(0.019, 0.023)
EIR	3.304***
	(3.239, 3.371)
(10x) Active Surv. Cov.	0.590***
	(0.573, 0.606)
0.2 ITN	0.151***
	(0.135, 0.169)
0.5 ITN	0.066***
	(0.058, 0.074)
0.8 ITN	0.040***
	(0.035, 0.045)
IIR 1	10.492***
	(9.858, 11.171)
IIR 10	16.272***
	(15.093, 17.547)
R0063	0.839***
	(0.751, 0.938)
R0065	0.443***
	(0.395, 0.497)
R0068	0.798***
	(0.714, 0.891)
R0111	0.870**
	(0.778, 0.972)
R0115	0.620***
	(0.554, 0.693)
R0121	1.041
	(0.932, 1.162)
R0125	1.362***
	(1.221, 1.519)
R0131	1.349***
	(1.209, 1.505)
R0132	1.865***
	(1.672, 2.080)
R0133	1.242***
	(1.114, 1.386)
R0670	1.065
	(0.954, 1.189)
R0674	2.535***
	(2.273, 2.828)
R0678	3.175***
	(2.846, 3.542)
Constant	1.295***
	(1.127, 1.487)
Observations	99,977
Log Likelihood	−27,763.340
Akaike Inf. Crit.	55,572.680

Note: *p<0.1; **p<0.05; ***p<0.01

Table 9: Linear regression of input model parameters on severity of resurgence

	Dependent variable:
	Severity
Case Management Coverage	-22.556^{***}
	$(-24.297, -20.814)$
EIR	25.159^{***}
	(24.916, 25.403)
(10x) Active Surv. Cov.	-22.664^{***}
	$(-23.213, -22.115)$
0.2 ITN	114.327^{***}
	(113.115, 115.538)
0.5 ITN	92.436^{***}
	(91.225, 93.647)
0.8 ITN	82.356^{***}
	(81.145, 83.568)
IIR 1	13.891^{***}
	(12.841, 14.940)
IIR 10	42.480^{***}
	(41.431, 43.529)
R0063	-6.729^{***}
	$(-8.996, -4.462)$
R0065	-9.763^{***}
	$(-12.029, -7.497)$
R0068	-13.066^{***}
	$(-15.332, -10.801)$
R0111	-0.152
	$(-2.418, 2.114)$
R0115	-3.142^{***}
	$(-5.407, -0.876)$
R0121	1.162
	$(-1.103, 3.428)$
R0125	7.219^{***}
	(4.953, 9.485)
R0131	3.641^{***}
	(1.376, 5.907)
R0132	9.744^{***}
	(7.478, 12.010)
R0133	4.068^{***}
	(1.802, 6.334)
R0670	2.115^{*}
	$(-0.150, 4.381)$
R0674	18.523^{***}
	(16.258, 20.789)
R0678	19.057^{***}
	(16.791, 21.323)
Constant	-84.231^{***}
	$(-86.380, -82.082)$
Observations	99,977
R^2	0.489
Adjusted R^2	0.489
Residual Std. Error	69.086 (df = 99955)
F Statistic	$4{,}558.459^{***}$ (df = 21; 99955)
Note:	*p<0.1; **p<0.05; ***p<0.01

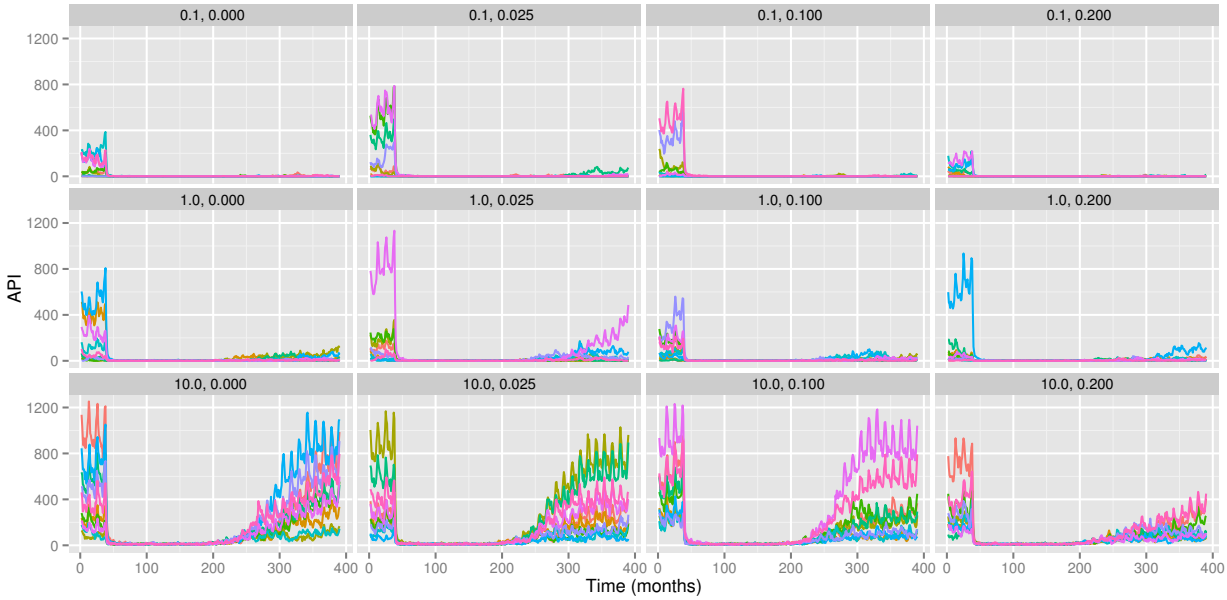


Figure 10: OpenMalaria simulation results for API per 1,000 per annum (Solomon Islands scenario) with an annual pre-intervention EIR of 0.1, case management coverage of 80%, and LLIN coverage of 80% during the period of vector control implementation. Each chart shows simulations results for varied levels of the infection importations rate and active surveillance (through quarterly mass screening and treatment (MSAT) coverage). These values are shown just above each chart in the form (IIR per thousand per year, proportion of population tested per quarter). Colors of lines within the chart represent various simulation runs with differing random seeds (thus capturing stochastic uncertainty). API is the annual parasite incidence computed at each time step and the x-axis is in months. LLINs are distributed at months 36, 72, 108, 144. Increased active surveillance starts immediately coincident with the last distribution of vector control.

4.4 Descriptive results of OpenMalaria simulation outputs: Solomon Islands Context

Simulation outputs allowed for the calculation of the time course of API, ABER and FOI in the Solomon Islands context. The results for API of some sample simulations are shown in Figure 10. Results of a subset of simulations for ABER are shown in Figure 11. Figure 12 shows the results of simulations of FOI for a subset of relevant simulation outputs.

Descriptive results are shown here in Tables 10–15 for elimination and resurgence by various input parameters. Most simulations (65%) resulted in "elimination" during vector control roll-out. However, a similar fraction (61%) of simulations showed resurgence after vector control withdrawal (Table 10). When results for resurgence and elimination were examined in bivariate analysis for background characteristics of simulation, occurrence of a resurgence was statistically significantly associated with infection importation rate, input EIR, active surveillance coverage, case management coverage, and the level of vector control coverage achieved and model variant (Tables 11–16). Elimination was associated with level of vector control coverage achieved, case management coverage, infection importation rate, input EIR and model variant (Tables 11–16).

Overall, there were 100,000 successfully completed simulations. In the majority of simulations (65%) the level of malaria transmission during vector control deployment met the criteria for elimination during vector control deployment. The majority of simulations (61%) also resulted in a resurgence after vector control withdraw (Table 10). Table 10 shows the proportion of simulations which resulted in elimination

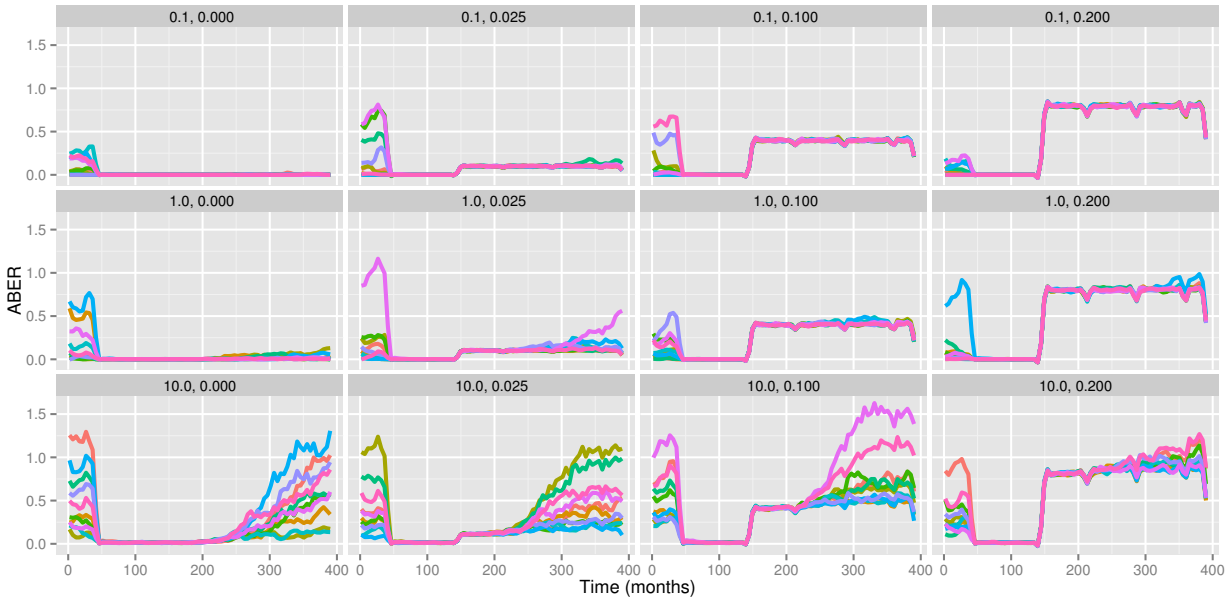


Figure 11: OpenMalaria simulation results for ABER (Solomon Islands scenario) with an annual pre-intervention EIR of 0.1, case management coverage of 80%, and LLIN coverage of 80% during the period of vector control implementation. Each chart shows simulations results for varied levels of the infection importations rate and active surveillance (through quarterly mass screening and treatment (MSAT) coverage). These values are shown just above each chart in the form (IIR per thousand per year, proportion of population tested per quarter). Colors of lines within the chart represent various simulation runs with differing random seeds (thus capturing stochastic uncertainty). ABER is the annual blood examination rate (smoothed to remove the visual effects of widely varying ABER between time periods with quarterly MSAT surveys) and the x-axis is in months. LLINs are distributed at months 36, 72, 108, 144. Increased active surveillance starts immediately coincident with the last distribution of vector control.

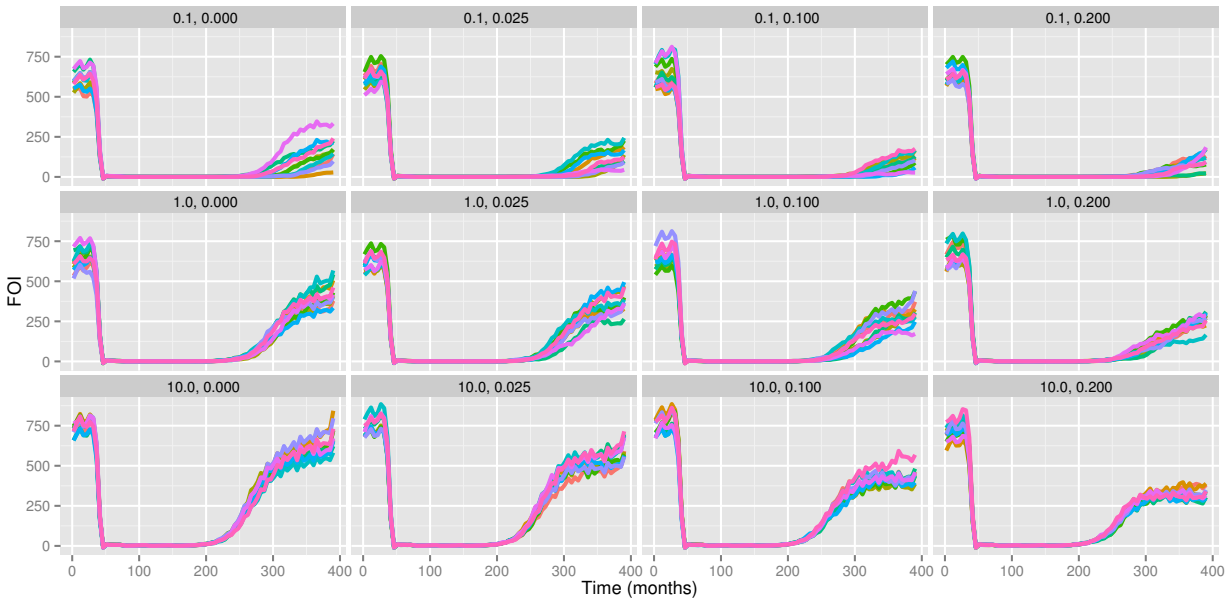


Figure 12: OpenMalaria simulation results for mFOI per 1,000 per annum (Solomon Islands scenario) with an annual pre-intervention EIR of 1, case management coverage of 80%, and LLIN coverage of 80% during the period of vector control implementation. Each chart shows simulations results for varied levels of the infection importations rate and active surveillance (through quarterly mass screening and treatment (MSAT) coverage). These values are shown just above each chart in the form (IIR per thousand per year, proportion of population tested per quarter). Colors of lines within the chart represent various simulation runs with differing random seeds (thus capturing stochastic uncertainty). mFOI is the molecular force of infection per 1,000 people per year and the x-axis is in months. LLINs are distributed at months 36, 72, 108, 144. Increased active surveillance starts immediately coincident with the last distribution of vector control.

and resurgence.

Variable	**Levels**	$\mathbf{n}_0$	$\%_0$	$\mathbf{n}_1$	$\%_1$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	35178	100.0	0	0.0	35178	35.2
	1	0	0.0	64822	100.0	64822	64.8
$p < 0.0001$	all	35178	100.0	64822	100.0	100000	100.0
Resurgence	0	1971	5.6	36664	56.6	38635	38.6
	1	33207	94.4	28158	43.4	61365	61.4
$p < 0.0001$	all	35178	100.0	64822	100.0	100000	100.0

Table 10: Simulation outputs for elimination and resurgence

Increasing coverage of ITNs during vector control deployment was associated with increased probabilities of elimination and as well as reduced probabilities of resurgence (Table 11).

Variable	**Levels**	$\mathbf{n}_0$	$\%_0$	$\mathbf{n}_{0.2}$	$\%_{0.2}$	$\mathbf{n}_{0.5}$	$\%_{0.5}$	$\mathbf{n}_{0.8}$	$\%_{0.8}$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	23953	95.8	9523	38.1	1671	6.7	31	0.1	35178	35.2
	1	1037	4.2	15467	61.9	23359	93.3	24959	99.9	64822	64.8
$p < 0.0001$	all	24990	100.0	24990	100.0	25030	100.0	24990	100.0	100000	100.0
Resurgence	0	1226	4.9	9532	38.1	13155	52.6	14722	58.9	38635	38.6
	1	23764	95.1	15458	61.9	11875	47.4	10268	41.1	61365	61.4
$p < 0.0001$	all	24990	100.0	24990	100.0	25030	100.0	24990	100.0	100000	100.0

Table 11: Simulation outputs for elimination and resurgence in terms of ITN coverage during vector control (Solomon Islands)

Changes in active surveillance coverage across the range tested was not statistically significantly related to the probability of elimination or resurgence. Though increasing active surveillance coverage did show a downward trend. Since active surveillance was not deployed during the period of vector control in these simulations the lack of any association with elimination during vector control is expected (Table 12).

Variable	**Levels**	$\mathbf{n}_0$	$\%_0$	$\mathbf{n}_{0.025}$	$\%_{0.025}$	$\mathbf{n}_{0.1}$	$\%_{0.1}$	$\mathbf{n}_{0.2}$	$\%_{0.2}$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	8873	35.2	8616	35.3	8839	35.1	8850	35.1	35178	35.2
	1	16327	64.8	15784	64.7	16361	64.9	16350	64.9	64822	64.8
$p = 0.95$	all	25200	100.0	24400	100.0	25200	100.0	25200	100.0	100000	100.0
Resurgence	0	8570	34.0	8639	35.4	10067	40.0	11359	45.1	38635	38.6
	1	16630	66.0	15761	64.6	15133	60.0	13841	54.9	61365	61.4
$p < 0.0001$	all	25200	100.0	24400	100.0	25200	100.0	25200	100.0	100000	100.0

Table 12: Simulation outputs for elimination and resurgence in terms of active surveillance coverage (Solomon Islands)

Changes in the level of case management coverage were associated with differences in both the probability of elimination and resurgence (Table 13).

Variable	**Levels**	$\mathbf{n}_{0.2}$	$\%_{0.2}$	$\mathbf{n}_{0.5}$	$\%_{0.5}$	$\mathbf{n}_{0.8}$	$\%_{0.8}$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	13358	39.8	11292	34.4	10528	31.3	35178	35.2
	1	20242	60.2	21508	65.6	23072	68.7	64822	64.8
$p < 0.0001$	all	33600	100.0	32800	100.0	33600	100.0	100000	100.0
Resurgence	0	9818	29.2	13051	39.8	15766	46.9	38635	38.6
	1	23782	70.8	19749	60.2	17834	53.1	61365	61.4
$p < 0.0001$	all	33600	100.0	32800	100.0	33600	100.0	100000	100.0

Table 13: Simulation outputs for elimination and resurgence in terms of case management coverage (Solomon Islands)

Pre-intervention EIR was strongly associated with probabilities of both elimination and resurgence. These associations showed trends in the expected directions with elimination much less likely to occur at higher input EIRs and resurgence much more likely to occur at higher baseline EIRs (Table 14).

Variable	**Levels**	$\mathbf{n}_{0.1}$	$\%_{0.1}$	$\mathbf{n}_{0.5}$	$\%_{0.5}$	$\mathbf{n}_{1}$	$\%_{1}$	$\mathbf{n}_{2}$	$\%_{2}$	$\mathbf{n}_{5}$	$\%_{5}$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	4125	20.6	5031	25.2	5916	29.6	8432	42.2	11674	58.4	35178	35.2
	1	15875	79.4	14969	74.8	14084	70.4	11568	57.8	8326	41.6	64822	64.8
$p < 0.0001$	all	20000	100.0	20000	100.0	20000	100.0	20000	100.0	20000	100.0	100000	100.0
Resurgence	0	13779	68.9	10079	50.4	7809	39.0	5292	26.5	1676	8.4	38635	38.6
	1	6221	31.1	9921	49.6	12191	61.0	14708	73.5	18324	91.6	61365	61.4
$p < 0.0001$	all	20000	100.0	20000	100.0	20000	100.0	20000	100.0	20000	100.0	100000	100.0

Table 14: Simulation outputs for elimination and resurgence in terms of input entomological inoculation rate (Solomon Islands)

Infection Importation Rate (IIR) was significantly associated with the probability of resurgence and elimination (Table 15).

Variable	**Levels**	$\mathbf{n}_{0.1}$	$\%_{0.1}$	$\mathbf{n}_{1}$	$\%_{1}$	$\mathbf{n}_{10}$	$\%_{10}$	$\mathbf{n}_{\text{all}}$	$\%_{\text{all}}$
Elimination	0	12319	37.0	11866	35.6	10993	33.0	35178	35.2
	1	21001	63.0	21454	64.4	22367	67.0	64822	64.8
$p < 0.0001$	all	33320	100.0	33320	100.0	33360	100.0	100000	100.0
Resurgence	0	19522	58.6	11849	35.6	7264	21.8	38635	38.6
	1	13798	41.4	21471	64.4	26096	78.2	61365	61.4
$p < 0.0001$	all	33320	100.0	33320	100.0	33360	100.0	100000	100.0

Table 15: Simulation outputs for elimination and resurgence in terms of infection importation rate per 1,000 per annum (Solomon Islands)

Model variant was also significantly associated with the probability of resurgence and elimination (Table 16).

Variable	Levels	n_{base}	$\%_{base}$	n_{R0063}	$\%_{R0063}$	n_{R0065}	$\%_{R0065}$	n_{R0068}	$\%_{R0068}$	n_{R0111}	$\%_{R0111}$	n_{R0115}	$\%_{R0115}$	n_{R0121}	$\%_{R0121}$	n_{R0125}	$\%_{R0125}$	n_{R0131}	$\%_{R0131}$	n_{R0132}	$\%_{R0132}$	n_{R0133}	$\%_{R0133}$	n_{R0670}	$\%_{R0670}$	n_{R0674}	$\%_{R0674}$	n_{R0678}	$\%_{R0678}$	n_{all}	$\%_{all}$
Elimination	0	2604	36.5	2866	40.1	2495	34.9	2474	34.6	2594	36.3	2341	32.8	2557	35.8	2340	32.8	2423	33.9	2355	33.0	2316	32.4	2480	34.7	2659	37.2	2674	37.5	35178	35.2
	1	4541	63.5	4279	59.9	4645	65.1	4671	65.4	4546	63.7	4804	67.2	4588	64.2	4800	67.2	4722	66.1	4785	67.0	4824	67.6	4665	65.3	4486	62.8	4466	62.5	64822	64.8
$p < 0.0001$	all	7145	100.0	7145	100.0	7140	100.0	7145	100.0	7140	100.0	7145	100.0	7145	100.0	7140	100.0	7145	100.0	7140	100.0	7140	100.0	7145	100.0	7145	100.0	7140	100.0	100000	100.0
Resurgence	0	2920	40.9	3059	42.8	3409	47.8	3117	43.6	2937	41.1	3050	42.7	2865	40.1	2532	35.5	2586	36.2	2364	33.1	2563	35.9	2785	39.0	2271	31.8	2177	30.5	38635	38.6
	1	4225	59.1	4086	57.2	3731	52.2	4028	56.4	4203	58.9	4095	57.3	4280	59.9	4608	64.5	4559	63.8	4776	66.9	4577	64.1	4360	61.0	4874	68.2	4963	69.5	61365	61.4
$p < 0.0001$	all	7145	100.0	7145	100.0	7140	100.0	7145	100.0	7140	100.0	7145	100.0	7145	100.0	7140	100.0	7145	100.0	7140	100.0	7140	100.0	7145	100.0	7145	100.0	7140	100.0	100000	100.0

Table 16: Simulation outputs for elimination and resurgence in terms of Model Variant (Solomon Islands Vector Parametrization). Details of the models variants are provided in [18].

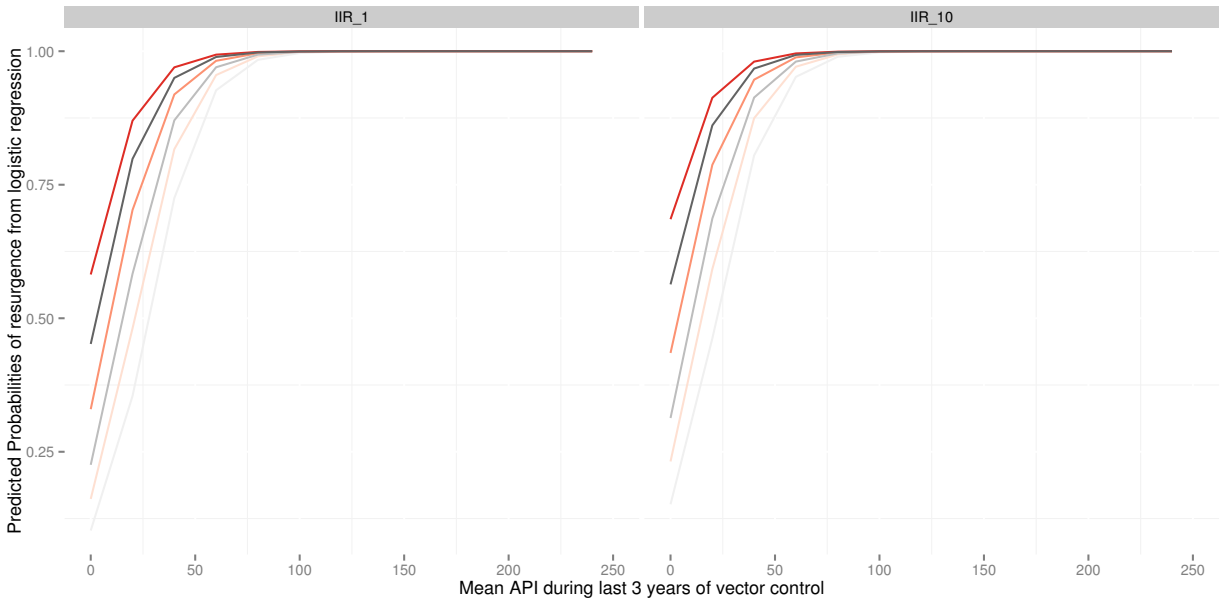


Figure 13: Predicted probabilities of resurgence based on regression results in Table 17 (Solomon Islands Scenario). Darker lines represent increasing EIR (0.1, 1, 2), while grey lines represent Active surveillance coverage of 1% per quarter and red lines represent Active surveillance coverage of 10% per quarter. All slopes here are for ITN coverage of 80%, Case management coverage of 50% and the base model variant.

4.5 Regression results: Solomon Islands

We applied logistic and linear regression using input parameters, and malaria outcomes during vector control interventions, of each simulation as predictors and the probability of resurgence post withdrawal of vector control as the outcome for logistic regression. Similarly we used the severity of resurgence for the outcome in the linear regression as previously defined for the analysis of the Kenya simulations. The results are summarized in Tables 17 & 18.

These results indicate that most parameters which were significant in bivariate analysis retained important predictive vale for the probability of a resurgence in multivariate analysis. Overall model results reinforce the importance of pre-intervention EIR, case management coverage, active surveillance coverage, infection importation and the level of control success during vector control deployment as major driving factors in predicting the probability of resurgence after withdrawal.

These logistic regression model results can be used to summarize the predicted probability of a resurgence occurring with varying levels of input parameters. Figure 13 shows the predicted probability of resurgence at varying levels of API, IIR, EIR and Active Surveillance coverage for the base model variant.

The predicted probability of resurgence is generally high for most parameter combinations and only falls below 0.25 for a set of simulations in which input EIR was less than 1, IIR was 1 per 1,000 per year, mean API during vector control deployment was below 25 per person per year and there was some level of active surveillance. While the definition of a safe probability of resurgence should be defined by local tolerance to risk and expected severity, it is unlikely that a probability of resurgence greater than 0.25 would fall under this definition.

Table 17: Logistic regression of input model parameters on resurgence (Solomon Islands)

	Dependent variable:	
	Resurgence	
Mean API During VC (per 1000)	1.082***	
	(1.077, 1.086)	
Case Management Cov.	0.038***	
	(0.035, 0.042)	
EIR	2.830***	
	(2.776, 2.885)	
(10x) Active Surv. Cov.	0.559***	
	(0.544, 0.574)	
0.2 ITN	0.262***	
	(0.232, 0.296)	
0.5 ITN	0.140***	
	(0.123, 0.159)	
0.8 ITN	0.093***	
	(0.081, 0.106)	
IIR 1	9.840***	
	(9.292, 10.425)	
IIR 10	15.403***	
	(14.305, 16.587)	
R0063	0.363***	
	(0.326, 0.403)	
R0065	0.256***	
	(0.229, 0.285)	
R0068	0.181***	
	(0.162, 0.202)	
R0111	0.284***	
	(0.255, 0.316)	
R0115	0.343***	
	(0.308, 0.382)	
R0121	0.310***	
	(0.279, 0.345)	
R0125	0.387***	
	(0.348, 0.430)	
R0131	0.626***	
	(0.562, 0.696)	
R0132	0.585***	
	(0.526, 0.650)	
R0133	0.783***	
	(0.704, 0.871)	
R0670	0.603***	
	(0.542, 0.671)	
R0674	0.430***	
	(0.386, 0.478)	
R0678	0.865***	
	(0.778, 0.963)	
Constant	2.843***	
	(2.455, 3.292)	
Observations		100,000
Log Likelihood	26	−29,467.250
Akaike Inf. Crit.		58,980.500
Note:		*p<0.1; **p<0.05; ***p<0.01

Table 18: Linear regression of input model parameters on severity of resurgence (Solomon Islands)

	Dependent variable:
	Severity
Case Management Coverage	-20.783^{***}
	$(-22.703, -18.864)$
EIR	28.872^{***}
	$(28.603, 29.140)$
(10x) Active Surv. Cov.	-27.918^{***}
	$(-28.524, -27.313)$
0.2 ITN	125.793^{***}
	$(124.457, 127.128)$
0.5 ITN	114.914^{***}
	$(113.579, 116.249)$
0.8 ITN	104.205^{***}
	$(102.869, 105.540)$
IIR 1	17.617^{***}
	$(16.461, 18.774)$
IIR 10	49.822^{***}
	$(48.666, 50.978)$
R0063	-23.737^{***}
	$(-26.235, -21.239)$
R0065	-30.010^{***}
	$(-32.509, -27.512)$
R0068	-32.958^{***}
	$(-35.456, -30.459)$
R0111	-36.839^{***}
	$(-39.337, -34.341)$
R0115	-24.585^{***}
	$(-27.084, -22.087)$
R0121	-29.339^{***}
	$(-31.837, -26.841)$
R0125	-22.064^{***}
	$(-24.562, -19.566)$
R0131	-16.834^{***}
	$(-19.332, -14.335)$
R0132	-18.154^{***}
	$(-20.652, -15.655)$
R0133	-10.975^{***}
	$(-13.473, -8.476)$
R0670	-17.170^{***}
	$(-19.669, -14.672)$
R0674	-21.107^{***}
	$(-23.605, -18.609)$
R0678	-0.092
	$(-2.590, 2.406)$
Constant	-77.644^{***}
	$(-80.013, -75.274)$
Observations	100,000
R^2	0.515
Adjusted R^2	0.515
Residual Std. Error	27 76.167 (df = 99978)
F Statistic	$5{,}051.379^{***}$ (df = 21; 99978)
Note:	*p<0.1; **p<0.05; ***p<0.01

5 Discussion and Limitations

We conducted Monte Carlo simulations to examine precision and bias associated with IIR measurement and ABER measurement; and a full factorial simulation experiment using the OpenMalaria simulation platform to identify determinants of potentially safe withdrawal of vector control. Overall the results indicate that only in a small minority of situations could withdrawal of vector control be expected to be safe (with a low probability of resurgence). These situations are characterized by low historic EIRs, low importation rates, highly successful vector control activities and high case management and surveillance coverage. In addition, we find that ABER and the infection importation rate may be useful indicators for measuring importation risk (or vulnerability) and surveillance coverage. While both have significant potential for bias in general the largest biases and the most important effects of their limited precision are likely to either result in conservative decisions, such as maintaining vector control, or to be of a small magnitude at relevant levels of the indicators. However, care should be taken to ensure that these indicators are measured in spatially (geographically) and temporally (seasonally) representative manners.

This study relies on Monte Carlo simulation and a stochastic agent-based simulation model of malaria epidemiology and immunology. While mathematical modelling techniques have been highly useful in malaria epidemiology and control, as well as program planing, they contain inherent simplifications of the real world. Model structures and assumptions can result in biases inherent in the models and limit their use for predicting real world outcomes. In particular, OpenMalaria does not explicitly model spatial dynamics and thus cannot simulate targeting interventions around index cases (such as focal vector control or screening and treatment) or control based on other local circumstantial knowledge. Such focal strategies are likely to be an important part of scaling back from universal coverage of vector control interventions in some situations and the results in this document do not explicitly capture this possibility.

We have chosen a particular definition of resurgence for the analysis of the simulation results in this experiment. We used this definition, both to be consistent with previous work [11], but also because it is strict and consistent with re-establishment of endemic transmission. Other definitions may produce different conclusions. One consequence of using a definition based on IIR is that higher IIR scenarios can experience significantly more cases without them being defined as resurgent. Another aspect of the definition is that it is limited to a defined temporal period. It is possible that the simulations we conducted that did not show resurgence would have shown resurgence in the months or years following the end of our simulation, although this is likely mitigated by the long length of monitoring (20 years) after the withdrawal of vector control in these simulations.

Finally these simulations assume that the receptivity of an area is stable. As such they do not include the potential effects of secular changes such as improved housing, general economic development, etc. on the likelihood of resurgence. Such changes might occur despite, or possibly as a consequence of changes in malaria transmission during vector control deployment [20].

While these simulation results suggest that there are a set of scenarios in which it is possible to withdraw vector control without a significant probability of resurgence, they suggest that these situations are limited. Furthermore, there is no guarantee that resurgence will not occur even when probability is low. Therefore, it is crucial that programs maintain surveillance coverage (both clinical as well as entomological) not only for the benefits related to preventing resurgence, but also so that malaria control and elimination programs which choose to scale back vector control are aware and prepared to make rapid responses should resurgence occur.

6 Conclusion

In areas with ongoing local malaria transmission the scale-back of vector control is likely to lead to resurgence and a return to pre-intervention levels of malaria parasite transmission and disease. The speed and severity of such a resurgence might be exacerbated by high pre-intervention malaria transmission, poor vector control coverage during interventions, and low case management coverage.

In areas in which local malaria transmission has been substantially reduced or interrupted, the scale-back of vector control is also associated with a high probability of resurgence for the vast majority of situations. The conditions which hold a low probability of resurgence include having a low pre-intervention EIR, high case management coverage, low importation and very successful control of transmission during intervention. The degree to which programs can safely plan to withdraw or scale back vector control must be determined by the tolerance of a program for risk of resurgence and its expected severity. When tolerance for the risk of resurgence is low, few situations would be a priori suitable for vector control withdrawal. If a 20% probability of resurgence is considered to be a threshold for safety, only scenarios with a pre-intervention EIR below 1 and moderate case management coverage (>50%) with successful achievement of universal vector control coverage (>80%) during the intervention phase were considered safe for withdrawal. This held for both Solomon Islands and Kenyan scenarios.

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When is it safe for malaria control and elimination programs to scale back vector control?

Literature Review and Simulation Study

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[5]Global Malaria Program, World Health Organization

16 September 2015

Background

- Universal coverage with vector control a costly (but effective) activity.
- Can transmission and burden reductions be maintained, even in the absence, or reduction, of vector control?
- Consultations during Global Technical Strategy development made clear the need for guidance to countries.

Questions

1. Are there situations in which reduction in coverage of vector control activities will *not* result in resurgent transmission?
2. What set of indicators is necessary to identify locations and times this might be safely undertaken?
3. What is the impact of the precision and bias associated with these measurements on estimates of the risk of resurgence?
4. What sets of measurements of these indicators would indicate that reductions in malaria vector control could be safely undertaken?

Methods

Overarching Literature Review

Precision and Bias Monte Carlo Simulation

Malaria Transmission OpenMalaria

Emulation Logistic Regression

Literature Review

- Searched Published and gray literature electronically for vector control "graduation" — "withdraw", "consolidation phase", "resurgence" and other related topics.
- Many observational studies on "resurgence"
- Few controlled studies
- No randomized control trials completed but one currently underway, in South Africa (*Pers. com.*, Immo Kleinschmidt).

Literature Review (continued)

- Resurgence reviewed in Cohen *et al.* systematic review of the published and gray literature to identify events of malaria resurgence.
- Reductions in funding most common cited reason for weakening of control program in question (49%). They state that:

  > *Reasons for funding reductions or cessation were not clear for all events, but in several, donors appear to have reallocated funding specifically* **because** *successful reductions in malaria burden had occurred (Emphasis Ours)*

Literature Review (continued)

- Other studies *e.g.*, Zambia and Benin shown that withdraw or relaxation of vector control efforts can lead, over short time periods, to resurgences in malaria prevalence, clinical incidence and transmission.
- Cohen *et al.* review is basically a case series
- Unfortunately few "controls" were found
- Best examples come from elimination settings

Literature Review — Ansari *et al.*

- One controlled study of withdrawal of vector control.
- Low transmission area – zoophilic vectors,
- Indoor residual spraying (IRS) with deltamethrin for 3 years at high intensity
- Withdrawn after annual parasite index (API) fell by nearly 90% to below one per 10,000 per year and follow-up studies were conducted over a period of 10 years.
- API & sporozoite positive rate (SPR) returned to levels comparable to an unsprayed control area by the end of study
- Nearly ten years of follow up.

Literature Review — GMEP

- During the Global Malaria Eradication Program (GMEP), transition from the "attack" to "consolidation" program phases.
- Initially, local API < 5 per 10,000 per annum and human (annual) blood examination rate (H(A)BER) $>$ 10%
- Later revised to < 1 per 10,000 per annum.

Indicators Investigated

- Infection Importation Rate
- Annual Blood Examination Rate
- EIR (pre-intervention)
- Annual Parasite Incidence

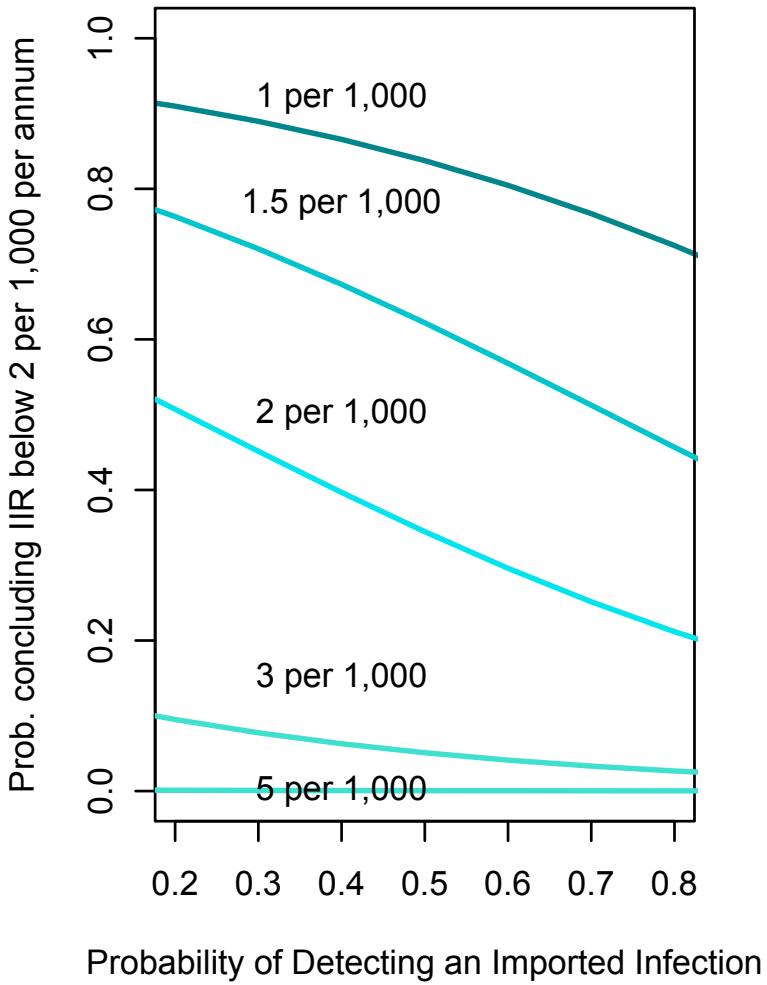
Simulation of Precision and Bias

- Infection Importation Rate (IIR)
  - Number of importations weekly: $N \sim \text{Poisson}(\text{True IIR})$
  - Observation $\sim \text{Binomial}(N, p)$
  - One year period (52 weeks) for 10,000 iterations

Infection Importation Rate

- Varied true IIRs (from 1 per 1,000 persons per annum to 5 per 1,000 persons per annum) and detection rates (from 20% to 80%).
- Tested a threshold of 2 per 1,000 per annum exact Poisson test with $\geqslant 90\%$ confidence.
- Applied logistic regression to estimate the predicted probability of concluding that IIR (based on the measurement) was below the threshold.

IIR Results



- Better detection implies that bias in determining IIR is low will be very conservative
- Danger of concluding this is low due to a poor surveillance system and misclassification

Simulation of Precision and Bias

- Annual Blood Examination Rate
  - Divergence between ABER and the total proportion of a population tested
  - Simulated a cohort with either independent probabilities of being tested in each round or without independence
  - Non-independent probability: $p_i \sim \text{Beta}(\alpha, \beta)$
  - Testing in one round: $p_{ij} \sim \text{Bernoulli}(p_i)$

Simulation of Precision and Bias

- The annual blood examination rate was calculated as

$$\text{ABER} = \frac{\text{Number of Tests Conducted}}{\text{Person-Years}} \quad (1)$$

- The proportion of the population actually tested was calculated as

$$\text{PT} = \frac{\text{Number of Individuals Tested}}{\text{Person-Years}} \quad (2)$$

ABER Results

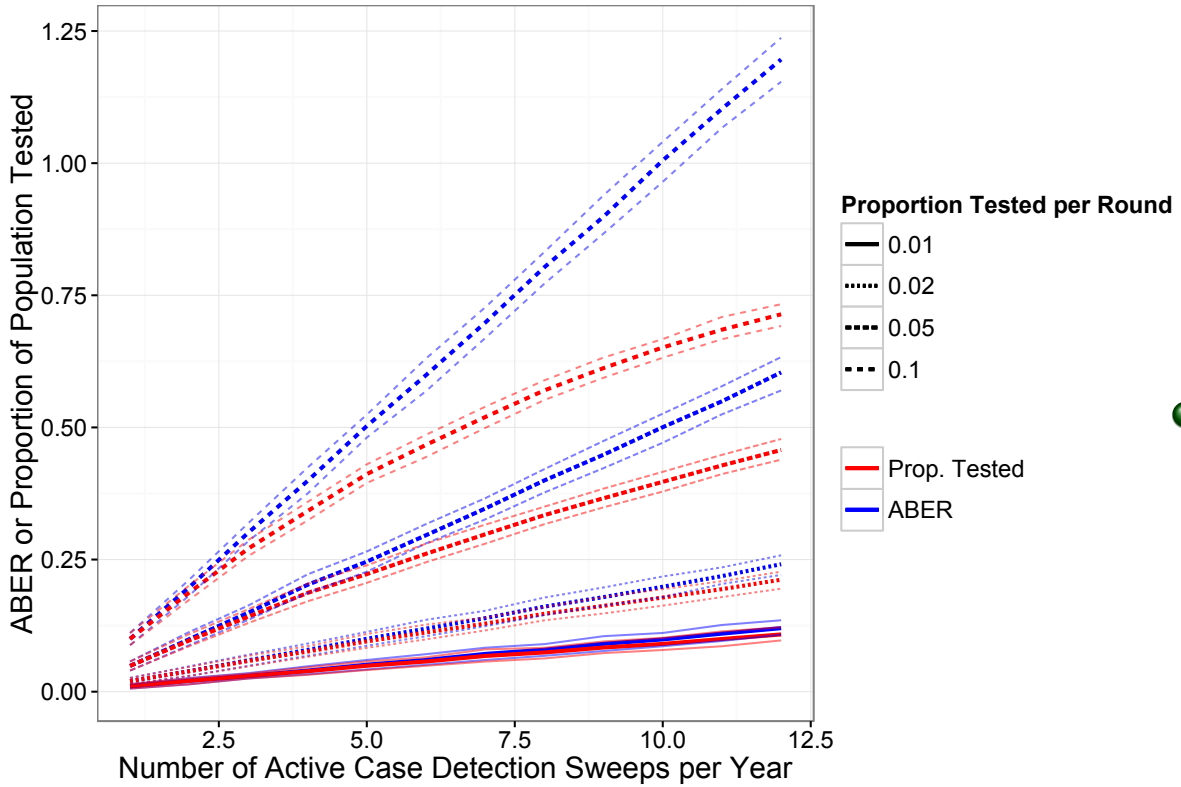


Figure: Simulation Results for Measurement of the Annual Blood Examination Rate

- ABER and the proportion tested by a surveillance system diverge at high values
- At low levels ABER is likely to be a reliable metric for the monitoring surveillance system coverage

OpenMalaria Background

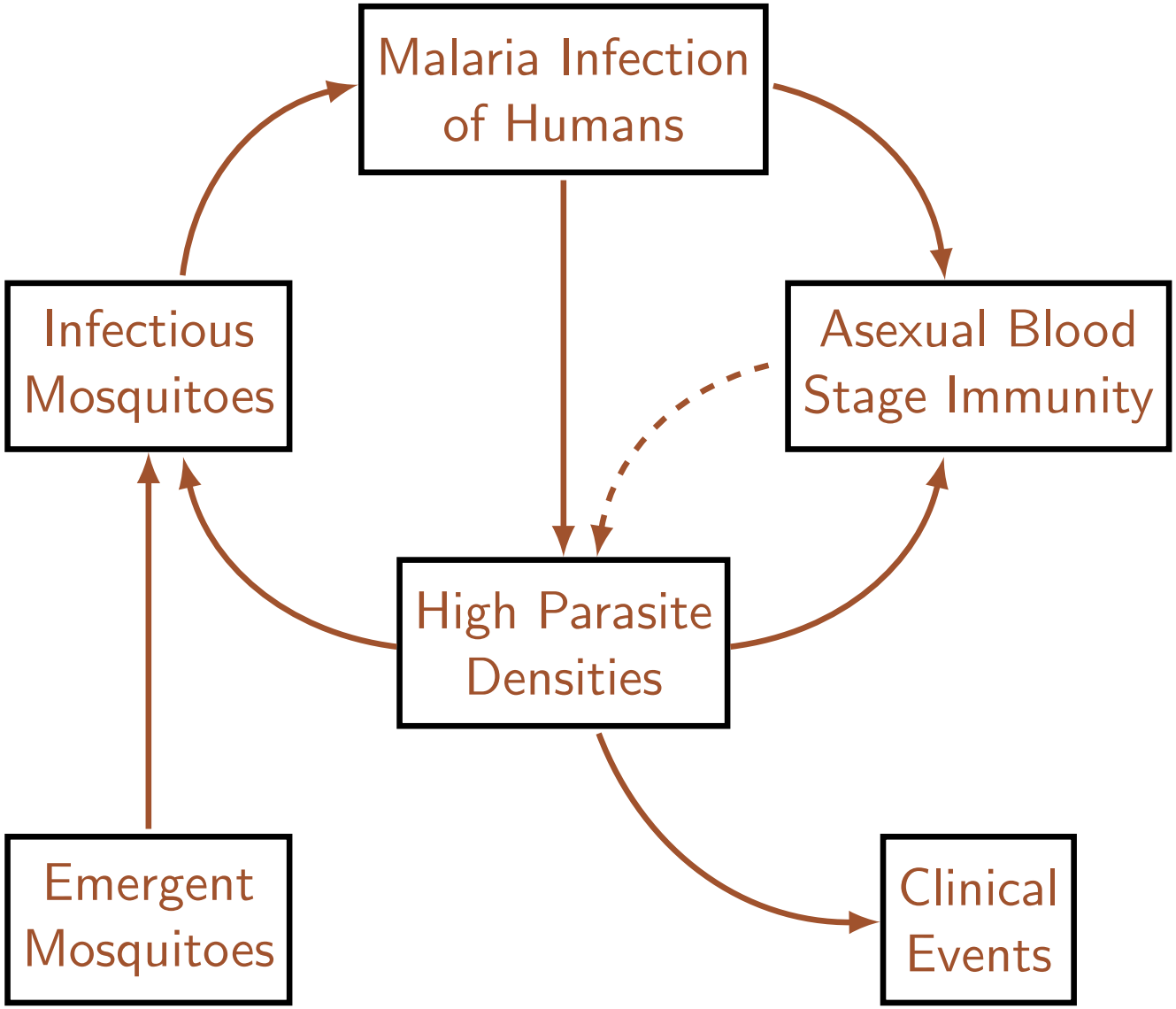


Figure: Schematic of the malaria transmission model

OpenMalaria Background

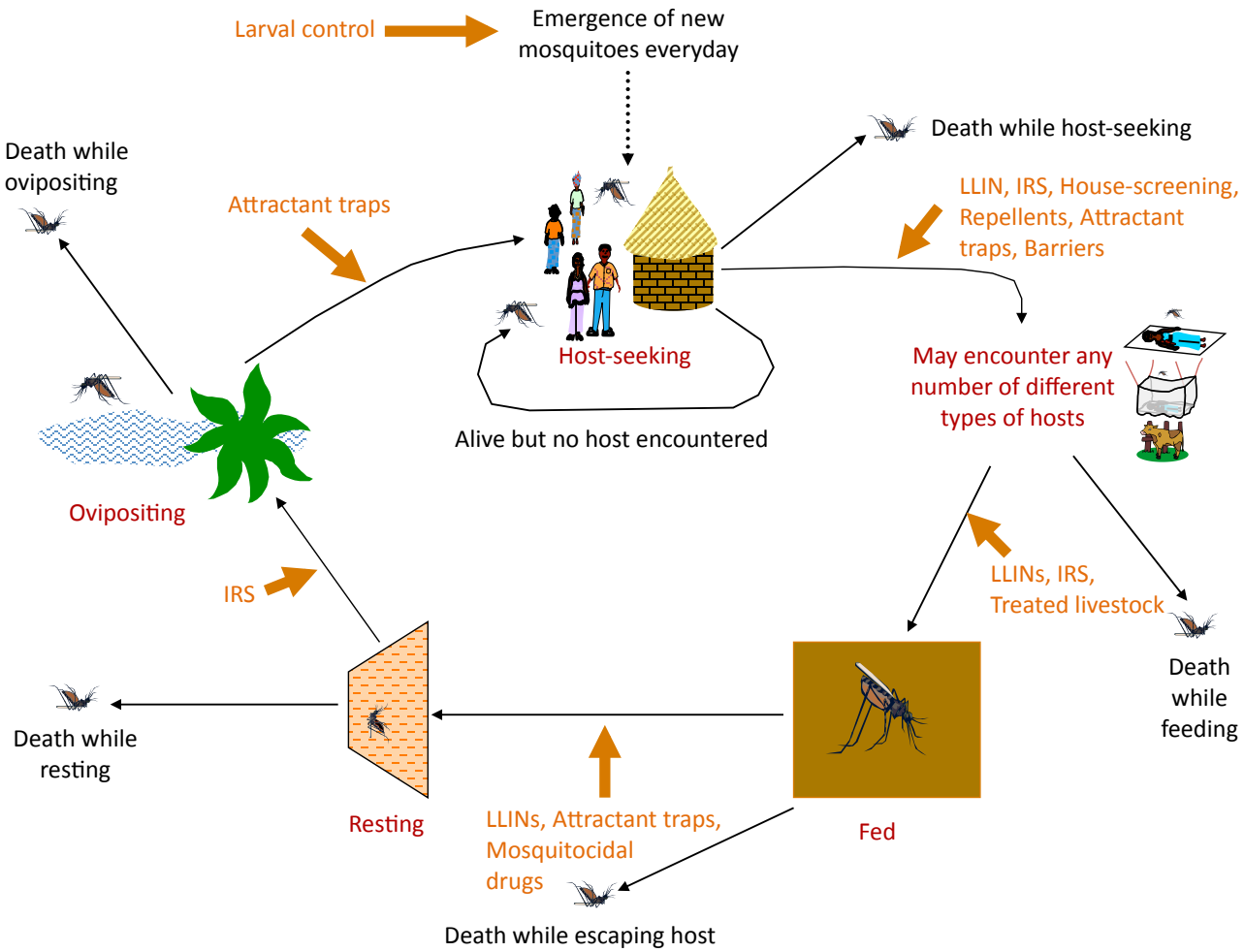
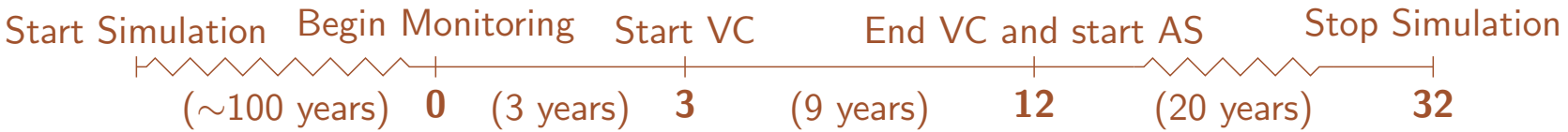


Figure: Schematic of mosquito feeding cycle dynamics including the effects of interventions.

Base Scenario and variants



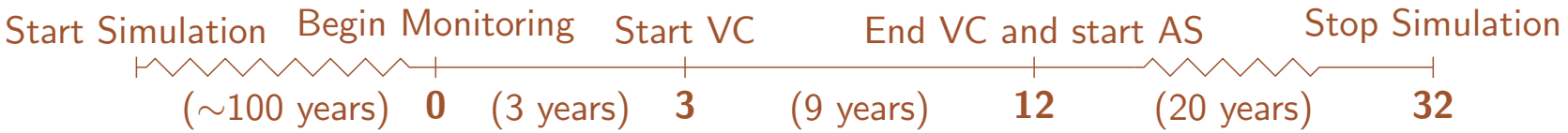
VC: Vector control

AS: Active surveillance

Baseline parameterizations for Western Kenya and Solomon Islands

- Human demographic profile
- Health systems settings
- Vector bionomics
- Seasonality
- Human population size of 10 000.

Base Scenario and variants



VC: Vector control

AS: Active surveillance

- Pre-intervention annual EIR of $\{0.1, 0.5, 1, 2, 5\}$.
- Coverage (proportion of population sleeping under) of LLINs of $\{0, 0.2, 0.5, 0.8\}$.
- IIR of $\{0.1, 1, 10\}$ per 1000 people per annum $\sim \text{Poisson}(\text{IIR})$

Base Scenario and variants

VC: Vector control

AS: Active surveillance

- Effective case management coverage of $\{0.2, 0.5, 0.8\}$.
- AS coverage of $\{0, 0.025, 0.1, 0.2\}$ 4 times a year using rapid diagnostic tests (RDTs).
- 14 model variants
- 10 random seeds

API Simulations for Kenya

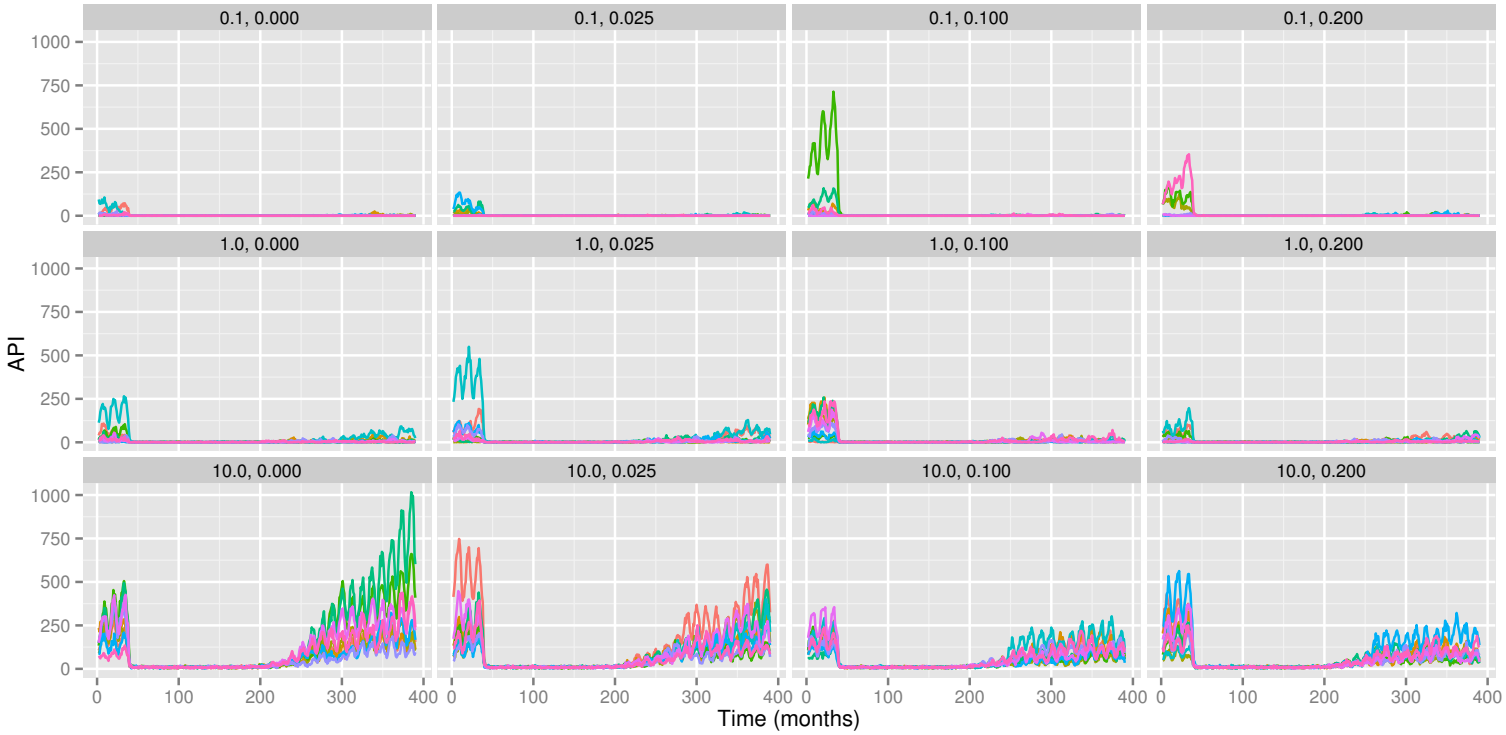
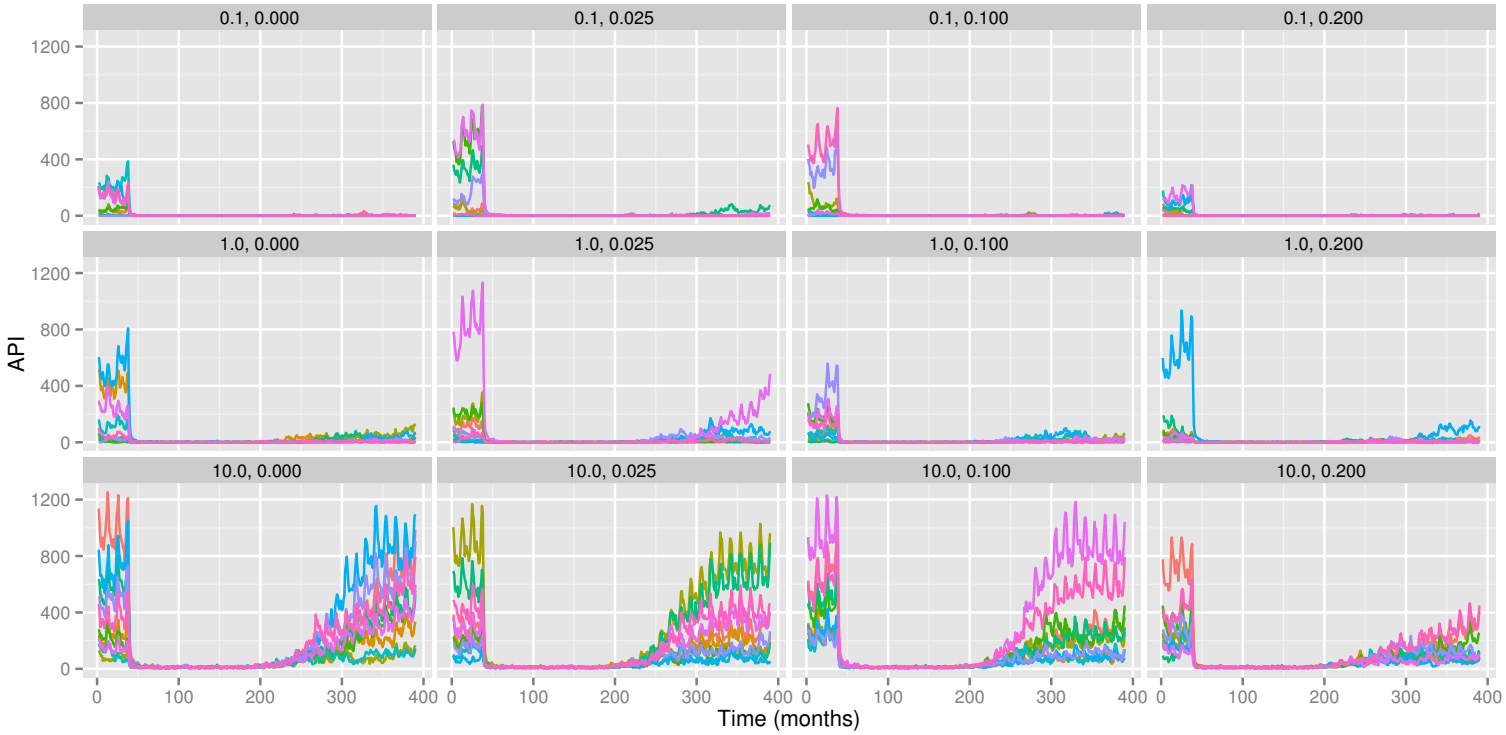


Figure: OpenMalaria simulation results for API per 1,000 per annum with an annual input EIR of 0.1, case management coverage of 80%, and ITN coverage of 80% during the period of Vector Control implementation. Each chart shows simulations results for varied levels of Infection Importations Rate and Active Surveillance (Quarterly Mass Screening and Treatment (MSAT) coverage)

API Simulations for Solomon Islands



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ABER Simulations for Kenya

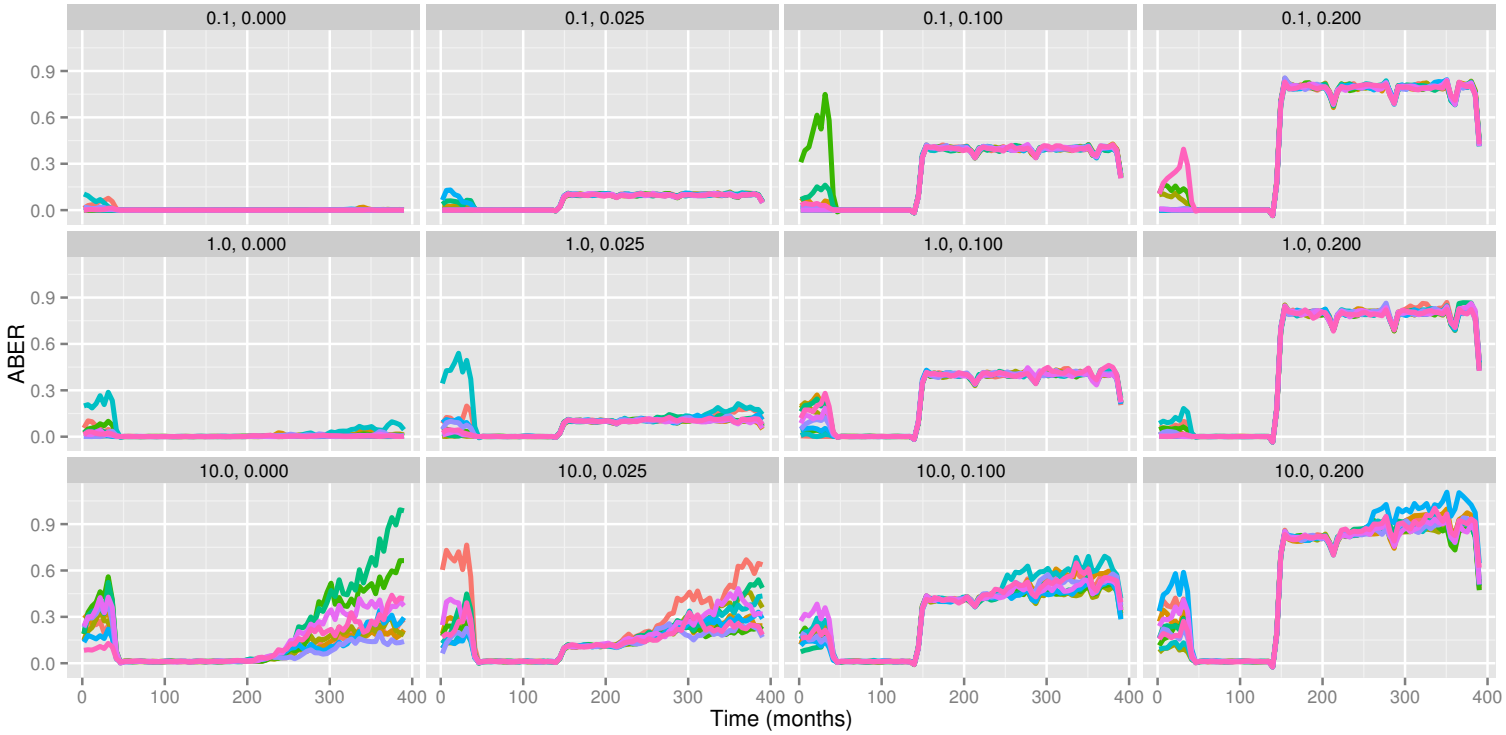


Figure: OpenMalaria simulation results for ABER with an annual input EIR of 0.1, case management coverage of 80%, and ITN coverage of 80% during the period of vector control implementation. Each chart shows simulations results for varied levels of infection importations rate (IIR) and active surveillance (quarterly mass screening and treatment (MSAT) coverage).

ABER Simulations for Solomon Islands

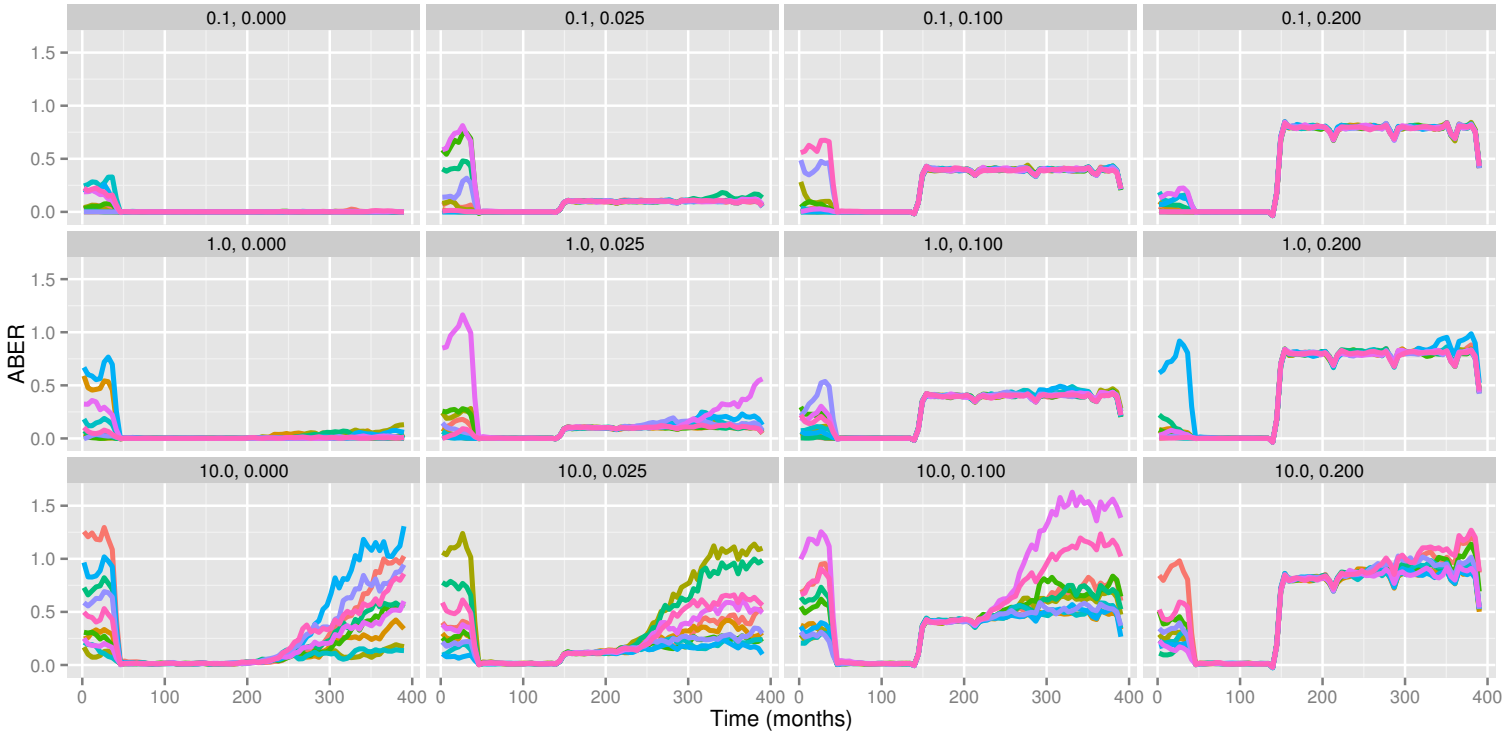


Figure: OpenMalaria simulation results for ABER with an annual input EIR of 0.1, case management coverage of 80%, and ITN coverage of 80% during the period of vector control implementation. Each chart shows simulations results for varied levels of infection importations rate (IIR) and active surveillance (quarterly mass screening and treatment (MSAT) coverage).

FOI Simulations for Kenya

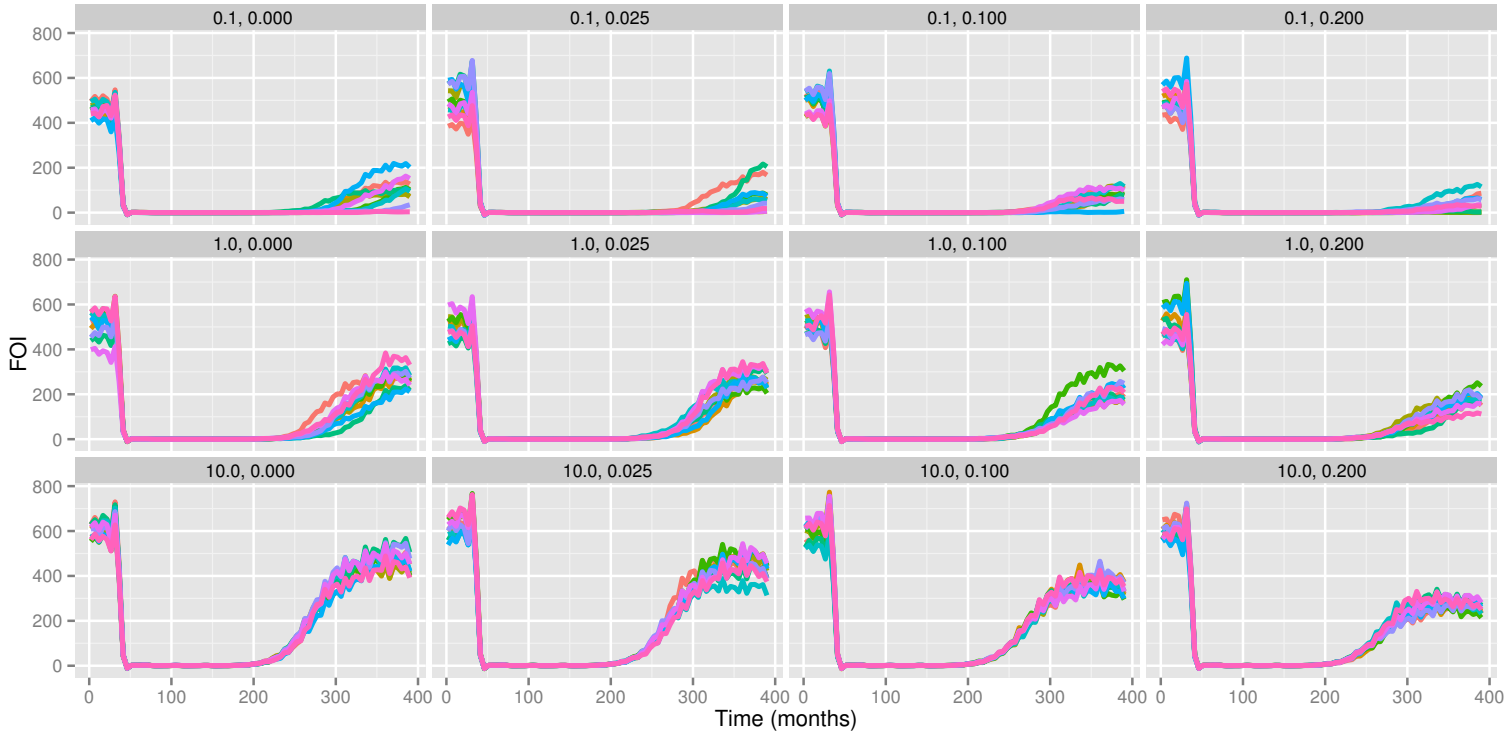
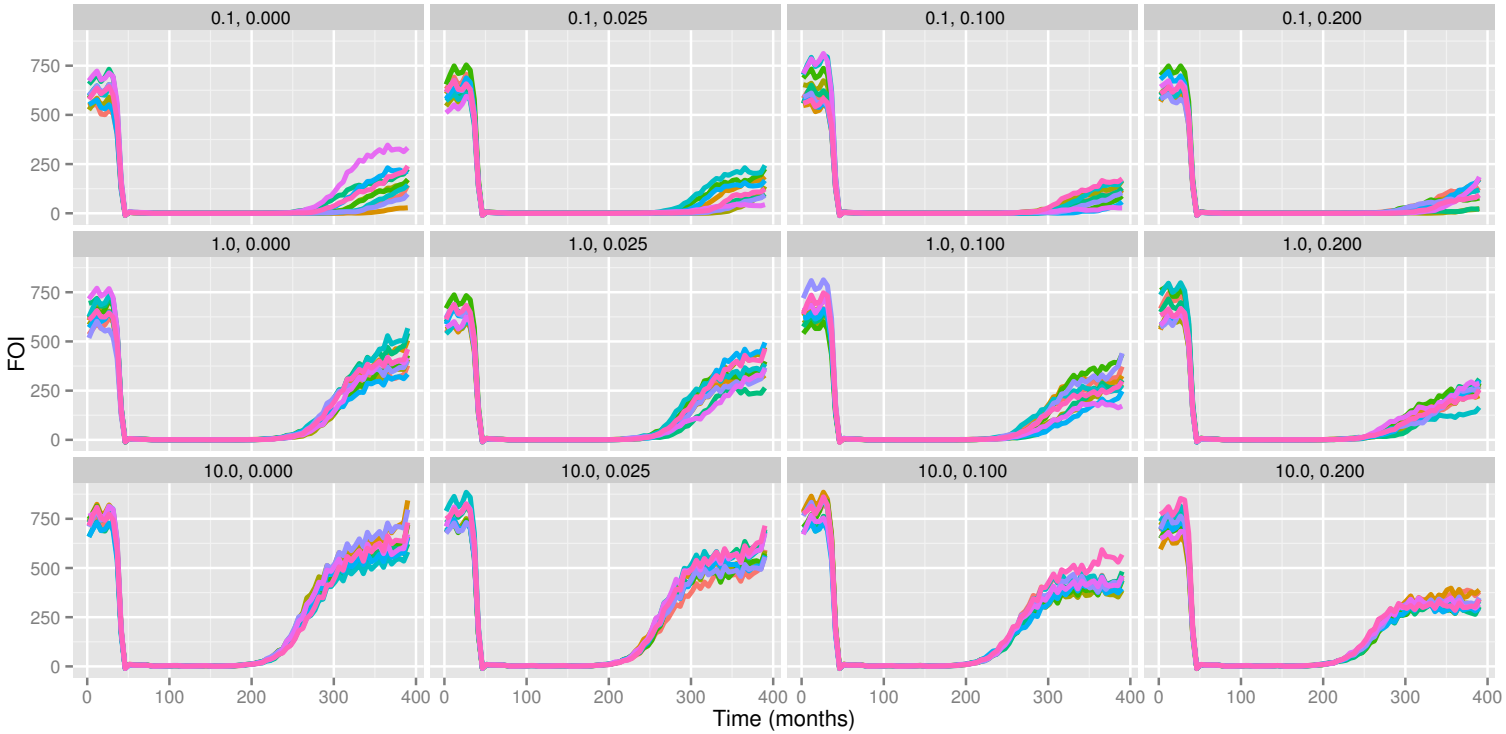


Figure: OpenMalaria simulation results for force of infection (FOI) per 1,000 per annum with an annual input EIR of 1, case management coverage of 80%, and ITN coverage of 80% during the period of Vector Control implementation. Each chart shows simulations results for varied levels of Infection Importations Rate and Active Surveillance (Quarterly Mass Screening and Treatment (MSAT) coverage).

FOI Simulations for Solomon Islands



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Resurgence Probability: Kenya

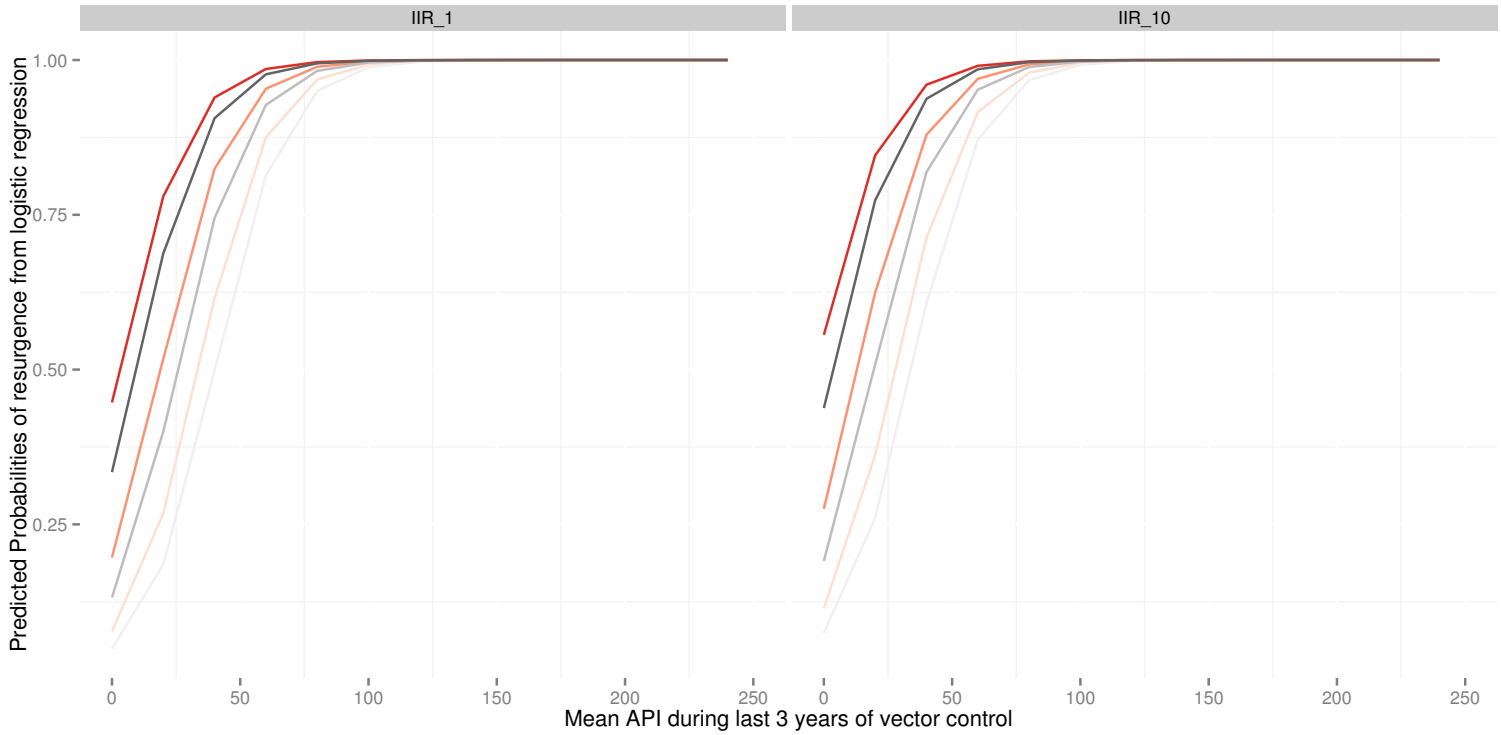
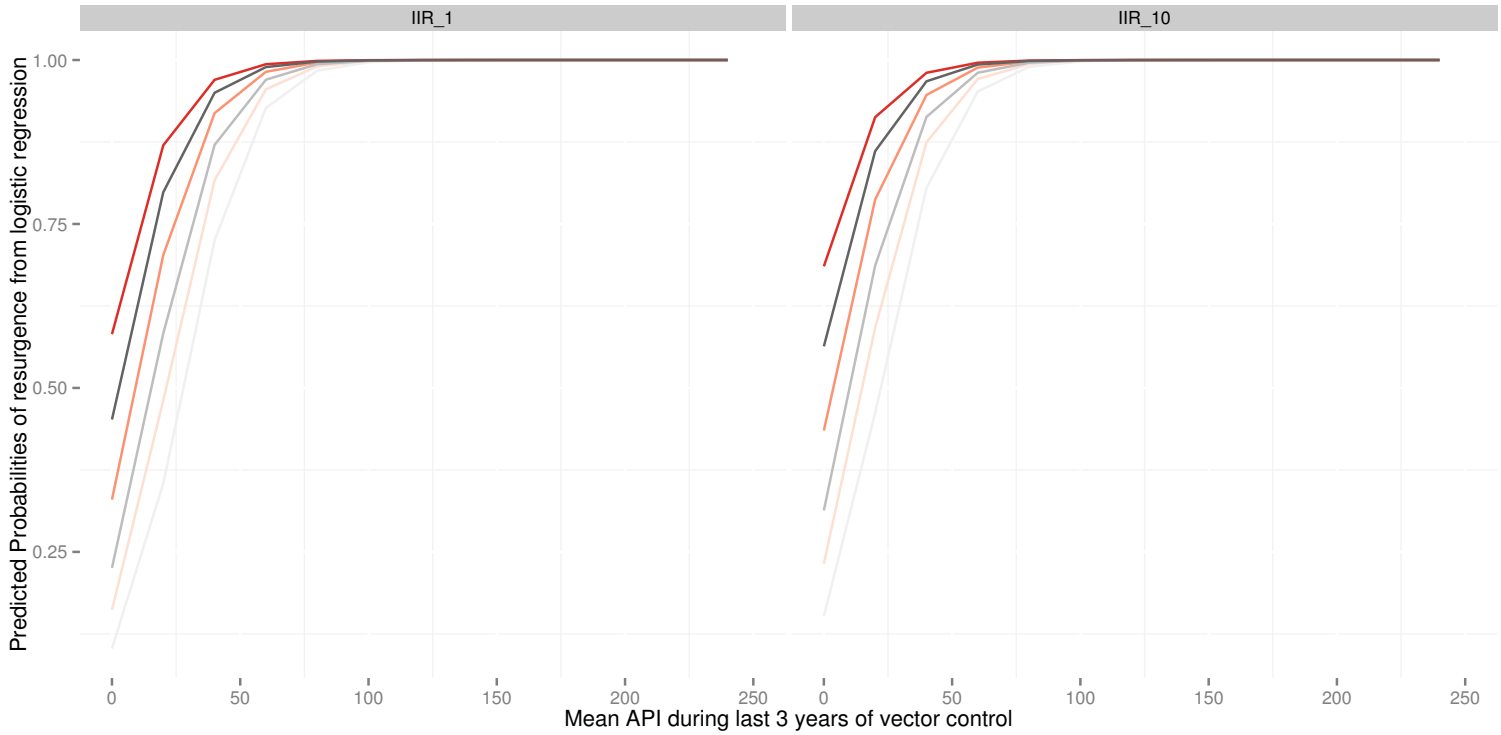


Figure: Predicted probabilities of resurgence based on logistic regression results. Darker lines represent increasing EIR (0.1, 1, 2), while grey lines represent Active surveillance coverage of 1% per quarter and red lines represent Active surveillance coverage of 10% per quarter. All slopes here are for ITN coverage of 80%.

Resurgence Probability: Solomon Islands



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Limitations

- Did not include vivax malaria
- Did not model spatially or temporally responsive strategies.
- Assumed stable receptivity

Recommendation 1

On the basis of this evidence, WHO recommends the following:

> *In areas*[1] *with ongoing local malaria transmission (irrespective of both the pre-intervention and the current level of transmission), the scale-back of vector control is not recommended. Universal coverage with effective malaria vector control of all persons at risk of malaria in such areas should therefore be pursued and maintained.*

[1] The minimum size of an area is determined by availability of reliable disaggregated disease surveillance data and feasibility for decisions on vector-control implementation.

Recommendation 2

On the basis of this evidence, WHO recommends the following:

> *In areas[2] where transmission has been interrupted, the scale-back of vector control should be based on a detailed analysis that includes assessment of receptivity[3], vulnerability and disease surveillance coverage, and capacity for case management and vector-control response.*

[2] The minimum size of an area is determined by availability of reliable disaggregated disease surveillance data and feasibility for decisions on vector-control implementation.

[3] The abundant presence of human-biting competent anopheline vectors a the existence of other ecological factors favouring malaria transmission.

Recommendation 3

On the basis of this evidence, WHO recommends the following:

> *Countries and partners are therefore requested to invest in health systems particularly in the strengthening of disease and entomological surveillance, as identification of such areas and the subsequent response, depends on the availability of this capacity.*

Global **Malaria** Programme

Risks associated with scale-back of vector control after malaria transmission has been reduced

NOVEMBER 2015

INFORMATION NOTE

BACKGROUND

Vector control is a core component of malaria prevention. This principally involves the use of either insecticide-treated mosquito nets (ITNs) (*1*) or indoor residual spraying (IRS) of insecticides (*2*). Larval source management (LSM) can be employed as a supplementary measure under specific conditions (*3*). WHO currently recommends universal coverage with effective vector control of all persons at risk of malaria. The population at risk is defined periodically on a sub-national level, and includes all persons in geographical areas or localities with ongoing malaria transmission.

Since 2000, substantial expansion of funding has enabled significant scaling up of malaria prevention, diagnostic testing and treatment. As a result, global malaria incidence declined by 37% and malaria mortality rates declined by 60% between 2000 and 2015 (*4*). Of the 106 countries that had malaria transmission in 2000, 102 are estimated to have reversed the incidence of malaria and achieved Millennium Development Goal Target 6C. Since 2000, four countries have been declared malaria free, and in 2014 there were 13 countries that reported zero locally-acquired cases with another six countries that reported fewer than 10 such cases.

Based on these achievements, the WHO *Global Technical Strategy for Malaria 2016–2030* lays the foundation for further significant reductions in mortality and incidence by at least 90% over the coming 15 years, with elimination of malaria projected for a further 35 countries (*5*).

WHO Member States have requested guidance on the circumstances under which it may be appropriate to scale-back vector control interventions to targeted deployment in specific geographic areas such as those with ongoing local malaria transmission. This request was largely prompted by the general decline in malaria transmission in most settings, and recognition that the epidemiology of malaria has been altered as a result of years of

World Health Organization

sustained, effective vector control. The result has been a general expectation that the discontinuation of vector-control implementation in such settings would be associated with a minimal risk of resurgence, and that such scale-back would be an appropriate way to reduce expenditure on malaria programmes.

To address this question, a better understanding is needed of the appropriate epidemiological and entomological conditions, or the surveillance and health systems requirements, that should be in place in order to consider and potentially plan for such scale-back of malaria vector control. This document is intended to provide guidance to countries and their partners on which areas or conditions are considered unsuitable for scale-back of malaria vector control.

HISTORICAL REVIEW AND MATHEMATICAL SIMULATIONS

In order to examine the impact of geographical scale-back of malaria vector control, a comprehensive review of historical evidence and mathematical simulation modelling using a range of epidemiological and intervention scenarios were undertaken (*6*).

Modelled scenarios examined the epidemiological implications of scale-back of ITNs[1] to no coverage under conditions of differing levels of:

- baseline (or pre-intervention) entomological inoculation rate (EIR) – using EIRs of 0.1, 0.5, 1, 2 or 5 infectious bites per person per year;
- infection importation rates – using rates of 0.1, 1 or 10 infections per 1000 persons per year;
- active case detection using 3-monthly mass screening and treatment undertaken at 0%, 2.5%, 10% and 20% coverage; and
- case management coverage – using coverage of 20%, 50% and 80% of all uncomplicated cases treated promptly and effectively.[2]

The results indicated that scale-back of malaria vector control was associated with a high probability of malaria resurgence, including for most scenarios in areas in which malaria transmission was very low or had been interrupted (i.e. no local transmission). Both the historical review and the simulation modelling clearly indicated that the risk of resurgence was significantly greater at higher values of EIR and importation rates, and lower coverage of active case detection and case management. Situations with a high probability of resurgence are likely to correspond most closely with malaria-endemic areas of sub-Saharan Africa.

The probability of resurgence was low only in scenarios with low historic EIRs, low infection importation rates, and high coverage of both active case detection and case management. Such scenarios correspond mainly to countries outside of sub-Saharan Africa that are currently experiencing very low malaria incidence.

1. Universal coverage is defined as one ITN for every two persons at risk of malaria; however, for the purpose of modelling, a population-wide estimate of 80% ITN usage was applied.
2. Five simulations run per model parameterization to include stochastic variation.

Outcomes from the literature analysis and simulation modelling were reviewed by the WHO Vector Control Technical Expert Group (VCTEG) at their meeting in March 2015 and were subsequently presented to the Malaria Policy Advisory Committee in September 2015. This document was formulated to provide clarification to countries on the risks associated with geographical scale-back of malaria vector control including in areas where malaria transmission has been reduced.

CONCLUSIONS

The evaluation indicated that, even in areas where there have been substantial reductions in malaria transmission,[3] in most situations, discontinuing vector control confers a high risk of malaria resurgence. This risk increases with increasing receptivity,[4] importation rates, low coverage of active disease surveillance and case management. This underscores the critical need for all countries with ongoing malaria transmission, and in particular those approaching elimination, to build and maintain strong capacity in disease and entomological surveillance and health systems. For example, the ability to respond to possible resurgences through vector control, relies on having the necessary entomological information (i.e. susceptibility status of vectors to insecticides as well as their biting and resting preferences). Such capacity is a pre-condition for evaluating the potential for geographical scale-back of vector control.

Precise measures of malaria receptivity and vulnerability,[5] and the levels of these parameters at which scale-back of vector control carries minimal risk of resurgence, remain to be comprehensively defined. Similarly, it is difficult to predict whether zero local transmission can be maintained in areas with moderate to high receptivity and vulnerability in the absence of vector control. Moreover, where there has been minimal change in receptivity, the stability of the malaria parasite–vector relationship following interruption of malaria transmission is not well understood. Further evaluations of the specific criteria for identifying areas where vector-control scale-back would carry a low risk of malaria resurgence are therefore required.

RECOMMENDATIONS

On the basis of this evidence, WHO recommends the following:

1. In areas[6] with ongoing local malaria transmission (irrespective of both the pre-intervention and the current level of transmission), the scale-back of vector control is not recommended. Universal coverage with effective malaria vector control (including the use of new vector control tools when they become available) of all persons in such areas, should be pursued and maintained.

3. It is difficult to develop a fixed definition for "substantial reduction", but an annual parasite index of <1 local case per 1000 population would indicate a low level of malaria transmission. At this level of malaria transmission, all cases should have been investigated and reliably classified as locally transmitted or imported.
4. The ability of an ecosystem to allow transmission of malaria.
5. The frequency of influx of infected individuals or groups and/or infective anophelines.
6. The minimum size of an area is determined by availability of reliable disaggregated disease surveillance data and feasibility for decisions on vector control implementation. The area is not necessarily based on administrative boundaries.

2. In areas[6] where transmission has been interrupted, the scale-back of vector control should be based on a detailed analysis that includes assessment of the receptivity and vulnerability, active disease surveillance system, and capacity for case management and vector control response.

3. Countries and partners should invest in health systems particularly in the strengthening of disease and entomological surveillance, as identification of areas for geographical scale-back as well as timely detection and appropriate response to resurgence depend on this capacity.

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Note

The guidance provided in this document has been superseded by more recent information. Please consult the Global Malaria Programme website for updates.

Malaria Policy Advisory Committee Meeting

16–18 September 2015, Geneva, Switzerland
Background document for Session 4

Malaria in pregnancy

WHO Evidence Review Group meeting report
WHO Headquarters, Geneva 13– 16 July 2015

Summary

Malaria in pregnancy (MiP) is a major, preventable cause of maternal morbidity and poor birth outcomes. To prevent the adverse outcomes of MiP, WHO recommends the use of insecticide-treated mosquito nets (ITNs), and effective case management of malaria and anaemia in pregnant women. In areas of moderate to high malaria transmission of sub-Saharan Africa, WHO also recommends intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP). In recent years, an alternative preventive strategy – consisting of intermittent screening and treatment in pregnancy (ISTp) using rapid diagnostic tests (RDTs) during antenatal care (ANC) visits – has been evaluated in several countries. Moreover, multiple studies have assessed the safety of using artemisinin-based combination therapies (ACTs) in the first trimester of pregnancy. Based on this new evidence, WHO convened a group of experts to develop recommendations on the efficacy and cost-effectiveness of (ISTp) compared to IPTp-SP for prevention of MiP, and on the safety of ACTs in early pregnancy.

The following conclusions and draft recommendations were proposed by the WHO evidence review group (ERG) for consideration by the WHO Malaria Policy Advisory Committee (MPAC).

1. IPTp-SP remains highly cost-effective in preventing the adverse consequences of malaria on maternal and fetal outcomes, and should thus be aggressively scaled up in line with the current WHO recommendations. IPTp-SP also remains effective in areas where quintuple-mutant haplotypes of Plasmodium falciparum to SP are highly prevalent.
2. An association between sextuple mutant haplotypes of *P. falciparum* and decreased low birth weight (LBW) has been reported in limited areas in the United Republic of Tanzania with very high SP resistance, in the context of observational studies using retrospective information about the assignment of SP. However, this has not been observed in other sub-Saharan countries in the context of randomized controlled trials with SP, and requires further investigation. In the limited geographical areas with very high SP resistance, it would be useful to evaluate, in pilot studies, the benefits and cost-effectiveness of adding, at the first ANC visit, a single RDT screening and treatment to the continued provision of IPTp-SP.
3. There is currently no evidence of a threshold level of malaria transmission below which IPTp-SP is no longer cost-effective. Therefore, in areas where IPTp-SP is implemented and transmission is reduced to low levels as a result of successful control strategies, WHO recommends continued implementation until the area has been targeted for malaria elimination by the national programme.
4. Recent studies have shown that IST with RDTs and ACTs of pregnant women at ANC resulted in a higher proportion of maternal infections and clinical malaria during

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pregnancy and lower mean birth weight compared with IPTp-SP. Further, being less cost-effective than IPTp-SP, ISTp with the currently available RDTs should not be recommended as an alternative to IPTp-SP.

6. Recent studies have shown that IPTp with dihydroartemisinin-piperaquine (DHA-PPQ) did not reduce LBW compared to IPTp-SP, but was more efficacious in reducing maternal malaria parasitaemia and anaemia at delivery, incidence of malaria infection and clinical malaria during pregnancy, stillbirths and early infant mortality (i.e. within 6–8 weeks). More research is needed to evaluate the impact of DHA-PPQ for IPTp on LBW, safety of repeated doses and adherence to the required 3-day regimen.
7. New evidence from 1025 pregnancies with confirmed artemisinin exposure in the first trimester indicates that artemisinins do not increase the risk of miscarriage, stillbirths or major congenital malformations compared to women with malaria treated with non-artemisinin regimens. Moreover, comparison of carefully documented and prospectively collected safety data on women exposed only to artemisinin-based treatment with data collected on women exposed only to quinine in the first trimester of pregnancy showed that artemisinin was associated with a significantly reduced rate of miscarriage compared to quinine. Therefore, the WHO recommendations for the treatment of clinical uncomplicated malaria episodes in women in the first trimester of pregnancy should be updated as follows: "Treat pregnant women with uncomplicated P. falciparum malaria with either the first-line ACT for 3 days or quinine and clindamycin for 7 days." Artemether-lumefantrine (AL) should be the preferred ACT, because most of the available data derive from AL exposure.
8. Although the evidence regarding the safety of ACTs in early pregnancy has been strengthened by the recent review, there is the need for continued monitoring of drug safety, birth outcomes and neonatal mortality. Moreover, there is also a need to monitor potential drug–drug interactions in HIV-infected pregnant women who are taking antiretroviral therapies and receive antimalarial medicines, as well as the risk of mother-to-child transmission.

Abbreviations

ACT	artemisinin-based combination therapy	ISTp	intermittent screening and treatment in pregnancy
AE	adverse event	ITN	insecticide-treated mosquito net
AL	artemether-lumefantrine	LBW	low birth weight
ANC	antenatal care	LLN	long-lasting insecticide-treated net
aPR	adjusted prevalence ratio	LMP	last menstrual period
AQAS	amodiaquine-artesunate	MiP	malaria in pregnancy
AS	artesunate	MQ	mefloquine
CEA	cost-effectiveness analysis	OR	odds ratio
CI	confidence interval	pc	post conception
DALY	disability adjusted life year	PCR	polymerase chain reaction
DHA	dihydroartemisinin	pLDH	parasite lactate dehydrogenase
dhfr	dihydrofolate reductase	POR	pooled odd ratio
dhps	dihydropteroate synthase	PPQ	piperaquine
ECG	electrocardiogram	PRR	pooled risk ratio
ERG	evidence review group	RCT	randomized controlled trial
HIV	human immunodeficiency virus	RD	risk difference
HR	hazard ratio	RDT	rapid diagnostic test
HRP2	histidine rich protein-2	RR	relative risk
ICER	incremental cost-effectiveness ratio	SP	sulfadoxine-pyrimethamine
IPTp	intermittent preventive treatment in pregnancy	WHO	World Health Organization

1 Background

Malaria in pregnancy (MiP) contributes significantly to maternal and neonatal mortality (1). Intermittent preventive treatment in pregnancy (IPTp) is a highly cost-effective preventive malaria intervention that significantly improves the health of mothers and their newborns in areas of moderate to high malaria transmission (2-6).

In October 2012, on the advice of the Malaria Policy Advisory Committee (MPAC) and the work of a dedicated evidence review group (ERG), WHO updated the policy for IPTp with sulfadoxine-pyrimethamine (SP) (7). The new policy recommends that women living in areas of moderate to high malaria transmission should receive IPTp-SP as early as possible in the second trimester, and at each scheduled antenatal care (ANC) visit thereafter, with SP doses given at least 1 month apart.

Since the updated IPTp policy was released, several countries throughout sub-Saharan Africa have updated their country policies to align with the new recommendations, but IPTp implementation still remains low. In 2013, the coverage of IPTp with two doses of SP was 43% (among 31 reporting countries) – well below national and international targets – and only 17% of all pregnant women received three or more doses of IPTp (among nine reporting countries) (8). It is of particular concern that, according to some preliminary estimates for 2014, coverage may be declining in some countries.

In 2013, the MPAC concluded that there was insufficient data to determine at what level of SP resistance IPTp-SP should be discontinued in the absence of an established and effective alternative, and to define the level of *Plasmodium falciparum* transmission at which IPTp-SP may cease to be cost-effective from a public health perspective (9).

Since then, several studies have been completed on the efficacy, safety, feasibility, acceptability and cost-effectiveness of alternative interventions to prevent the consequences of MiP, including intermittent screening and treatment in pregnancy (ISTp). This intervention uses rapid diagnostic tests (RDTs) for screening of pregnant women, and treatment of RDT-positive women with an effective combination therapy. The impact of ISTp has been studied with SP, amodiaquine-artesunate (AQAS), dihydroartemisinin-piperaquine (DHA-PPQ) and artemether-lumefantrine (AL). In addition:

- meta-analyses have been completed to evaluate:
    - the impact of antifolate resistance and level of malaria transmission on the effectiveness of IPTp-SP;
    - the efficacy of IPTp-SP compared to ISTp-AL and ISTp-DHA-PPQ in areas with different levels of SP resistance and transmission intensity; and
- studies evaluating the efficacy and safety of DHA-PPQ for IPTp have recently been completed.

During recent years, a growing body of evidence has accumulated on the clinical safety of the artemisinin derivatives in the first trimester of pregnancy, and of the efficacy of different artemisinin-based combination therapies (ACTs) in treatment of uncomplicated MiP. A series of prospective cohort studies of pregnant women have been completed to assess pregnancy outcomes of women with malaria exposed to different artemisinin derivatives or to quinine during the first trimester of pregnancy, compared to pregnant women not exposed to either malaria or antimalarial treatment.

2 Rationale, objectives and process

2.1 Rationale

To review these studies and to update WHO recommendations with the most efficacious and cost-effective interventions for the prevention of the adverse maternal and infant consequences of MiP, the WHO Global Malaria Programme (GMP) convened an ERG with a specific focus on the efficacy of ISTp compared with IPTp, and the safety of artemisinin derivatives in early pregnancy.

2.2 Objectives

The specific objectives of the meeting in relation to potential alternatives to IPTp-SP were as follows:

1. Review all available published and unpublished reports on the efficacy and safety of ISTp compared to IPTp for prevention of the adverse consequences of MiP.
2. Review all available reports on the acceptability of ISTp under trial conditions.
3. Review results of cost-effectiveness analyses (CEA) of ISTp.
4. Review the recent evidence on the effect of submicroscopic infections on maternal and infant outcomes.
5. Review available published and unpublished reports on the impact of SP resistance on the effectiveness of IPTp-SP.
6. Review results of recently completed clinical trials evaluating the efficacy and safety of DHA-PPQ for IPTp.
7. Based on the evidence reviewed, consider whether either ISTp or IPTp-DHA-PPQ could be recommended as a potential alternative to IPTp-SP in some areas with high SP resistance and/or very low transmission.

The specific objectives of the meeting in relation to the safety of ACTs in early pregnancy were as follows:

1. Review the evidence of embryotoxicity of artemisinin derivatives from animal studies.
2. Review available published and unpublished reports on exposures to artemisinin derivatives in the first trimester of pregnancy.
3. Review results of recent clinical trials evaluating the efficacy and safety of different ACTs for malaria treatment in the second and third trimester of pregnancy.
4. Based on the evidence reviewed, consider whether the current WHO recommendations on use of ACTs in pregnancy could be updated.

2.3 Process

Data were presented as pre-reads and oral presentations for each of the following topics:

1. ISTp compared to IPTp-SP in west and east Africa.
2. Acceptability of ISTp under trial conditions.
3. Cost-effectiveness of ISTp.
4. Effects of submicroscopic infections on maternal and infant outcomes.
5. Impact of SP resistance and malaria transmission on IPTp-SP effectiveness.
6. Evaluation of DHA-PPQ for IPTp.
7. Embryotoxicity of artemisinin derivatives in animal studies.
8. Safety of artemisinin exposure in the first trimester of pregnancy.

9. Efficacy and safety of ACTs for malaria treatment in the second and third trimester of pregnancy.
10. General considerations on use of antimalarial medicines in pregnancy.
11. Report of increased mother-to-child transmission of HIV following IPTp with mefloquine (MQ).

Preference was given to studies that were published or accepted for publication in peer-reviewed journals. For a few studies, the manuscript in pre-publication status was accepted. The full list of pre-reads is at Annex 1. Participants came from four different groups: presenters of the evidence, independent reviewers, observers and WHO Secretariat (the list of participants is at Annex 2). The participation of observers complied with WHO rules of observership.[1] All declarations of interest of the reviewers were assessed by the WHO Secretariat, and none were found to have any conflict of interest that could preclude their participation in assessment of the evidence presented. All participants contributed to the sessions in plenary and working groups, but only the independent reviewers and WHO Secretariat attended a final closed session to elaborate the recommendations of the meeting.

The key conclusions emerging from the topics are presented in boxes at the end of the respective sections of the report. The general conclusions and recommendations of the meeting, reviewed and agreed among the independent reviewers, are presented in the summary, and as the last section of the report (Section 4).

3 Evidence reviewed

3.1 Studies on ISTp compared with IPTp-SP in west and east Africa

The results of four randomized controlled trials (RCTs) evaluating ISTp among HIV-negative pregnant women from areas with low SP resistance in west Africa and from areas with high SP resistance in east and southern Africa were presented. The results of a pooled analysis of the two trials in east Africa were also presented and discussed.

3.1.1 RCT in Ghana

The first study was designed as a three-arm **open-label non-inferiority** RCT comparing ISTp with AQAS; ISTp with SP; and standard two-dose IPTp-SP (10). The trial was conducted in 2007–2008 and included **3333 pregnant women** from **Ghana** of **unknown HIV status**. The primary endpoint was the prevalence of severe maternal anaemia (defined by a haemoglobin level <8 g/dL) at the third trimester of pregnancy. All women received a long-lasting insecticide-treated net (LLN). Women on the ISTp groups were screened for malaria infection with an RDT based on parasite lactate dehydrogenase (pLDH). Those found to be positive received either SP or AQAS; only the first dose of the treatment was directly observed. At 36–40 weeks of gestation, the prevalence of asymptomatic parasitaemia was 12.1% in study women overall, and was similar in all treatment groups. The risk of third-trimester severe anaemia or low birth weight (LBW) did not differ significantly between the three treatment groups regardless of gravidity.

ISTp with AQAS or SP was not inferior to two-dose SP-IPTp in reducing the risk of LBW (risk difference, RD=–1.17 [95% CI: –4.39–1.02] for IST-SP versus SP-IPTp and RD=0.78 [95% CI: –2.11–3.68] for IST-AQAS versus SP-IPTp) **and third-trimester severe maternal anaemia** (RD=0.29 [95% CI: –0.69–1.30] for IST-SP versus SP-IPTp and RD=–0.36 [95% CI: –1.12–0.44] for IST-AQAS versus SP-IPTp). The frequency of reported general weakness as an adverse event (AE)

1. See http://www.who.int/malaria/mpac/rulesofobservership/en/

was significantly higher in the ISTp-AQAS than in the other treatment groups. No information on placental infection prevalence was available. The results of this first study suggest that ISTp could be a promising strategy for malaria prevention in pregnancy in some areas but need to be confirmed in larger multicentre trials.

3.1.2 RCT in Gambia, Mali, Burkina Faso and Ghana

A subsequent **multicentre,** open, individually randomized, **non-inferiority RCT** was conducted in **four west African countries** with a low prevalence of resistance to SP (Gambia, Mali, Burkina Faso and Ghana) to evaluate the efficacy and safety of **ISTp with AL compared with IPTp-SP** (11). The trial was conducted in 2010–2012 and included 5354 HIV-negative pregnant women. Participants in the IPTp-SP group received SP on two or three occasions, whereas women in the ISTp group were screened two or three times with a histidine rich protein-2 (HRP2)/pLDH combination (Pf/Pan) RDT and, if positive for malaria, treated with AL. All women received an LLN.

ISTp-AL was non-inferior to IPTp-SP in preventing LBW, anaemia and placental malaria, the primary trial endpoints. No significant differences were found between groups in the prevalence of LBW (15.1% and 15.6% in the IPTp-SP and ISTp-AL groups, respectively; odds ratio, OR=1.03 [95% CI: 0.88–1.22]) and in the mean haemoglobin concentration at the last ANC clinic visit (10.97 g/dL and 10.94 g/dL in the IPTp-SP and ISTp-AL groups, respectively; mean difference: –0.03 g/dL [95% CI: –0.13–0.06]). Active malaria infection of the placenta was found in 24.5% and in 24.2% of women in the IPTp-SP and ISTp-AL groups, respectively (OR=0.95 [95% CI: 0.81–1.12]).

More women in the ISTp-AL than in the IPTp-SP group presented with malaria parasitaemia and clinical malaria between routine ANC visits (310 versus 182 episodes, rate difference: 49.4 per 1000 pregnancies [95% CI: 30.5–68.3]). Unscheduled visits were also more frequent among women in the ISTp-AL group (1204 visits) than in those in the IPTp-SP group (988 visits) (*P*=0.001). These findings suggest that, in the absence of an effective alternative drug to SP for IPTp, ISTp-AL could be considered a potential alternative to IPTp in areas where SP resistance is high or malaria transmission very low.

3.1.3 RCT in Malawi

The third study evaluating ISTp was conducted **in an area of high SP resistance from Malawi** between 2011 and 2013 (12). The study was designed as an open-label two-arm individually randomized superiority trial and included 1873 HIV-negative women (1155 primi+ secundigravidae [paucigravidae], 718 multigravidae). Participants were randomized to receive either IPTp-SP or ISTp-DHA-PPQ at each ANC visit (three or four visits were scheduled in the second and third trimester, 4–6 weeks apart). All women received an LLN, and all treatment doses in both arms were supervised. The prevalence of adverse birth outcome (defined by a composite of LBW, preterm birth and small for gestational age) was similar in both arms: ISTp-DHA-PPQ=29.9%, IPTp-SP=28.8%, RD=1.08% (95% CI: –3.25–5.41); relative risk (RR)=1.04 (0.90–1.20), *P*=0.625;paucigravidae: RR=1.10 [0.92–1.31], *P*=0.282; multigravidae RR=0.92 [0.71–1.20], *P*=0.543.

The prevalence of malaria at delivery was higher in the ISTp-DHA-PPQ arm (48.7% versus 40.8%): RD=7.85 (3.07–12.63); RR=1.19 (1.07–1.33), *P*=0.007 (paucigravidae: RR=1.16 [1.04–1.31], *P*=0.011; multigravidae: RR=1.29 [1.02–1.63], *P*=0.037). **Fetal loss was more common with ISTp-DHA-PPQ** (2.6% versus 1.3%; RR=2.06 [1.01–4.21], *P*=0.046) and highest among non-DHA-PPQ-recipients (3.1%) in the ISTp-DHA-PPQ arm. Consequently, **ISTp was not superior to IPTp-SP in this area with high SP resistance**, and it was associated with higher fetal loss and more malaria at delivery.

3.1.4 RCT in Kenya

The fourth study was an **open-label three-arm randomized superiority trial** conducted in an area of **western Kenya** with high malaria transmission and high levels of SP resistance (4). Between August 2012 and June 2014, 1546 HIV-negative pregnant women of 16–32 weeks gestation were randomized to receive **ISTp-DHA-PPQ, IPTp-DHA-PPQ or IPTp-SP** three to four times during pregnancy at least 1 month apart. The primary outcome was malaria infection at delivery (composite of peripheral or placental parasitaemia detected by placental histology, microscopy or RDT). The results of the comparison between IPTp-SP versus ISTp-DHA-PPQ are presented here. The comparison with IPTp-SP is presented later in this document.

The **prevalence of malaria infection at delivery was not lower in the ISTp-DHA-PPQ** than the IPTp-SP arm (12.6% versus 10.2%, RR=1.23 [0.86–1.77], *P*=0.26). There were **no significant differences in adverse birth outcomes** (composite of small for gestational age, LBW or preterm birth) between study arms (ISTp-DHA-PPQ versus IPTp-SP: 13.5% versus 10.0%, RR=1.35 [0.93–1.96], *P*=0.12), fetal loss (2.4% versus 3.8%, RR=0.65 [0.31–1.36], *P*=0.25), and infant mortality by 6–8 weeks (1.3% versus 2.9%, RR=0.46 [0.18–1.20], *P*=0.11). **The incidence of malaria infection and clinical malaria were significantly higher in the ISTp-DHA-PPQ arm** (malaria infection incidence: 232 versus 192 per 100 person years, IRR=1.21 [1.03–1.41], *P*=0.02; clinical malaria: 53 versus 38 per 100 person years, RR=1.41 [1.00–1.98], *P*=0.05 [*P*=0.04 in paucigravidae]). These findings indicate that **at the current levels of RDT sensitivity, ISTp is not a suitable alternative to IPTp-SP in the context of high SP resistance and malaria transmission**.

3.1.5 Individual participant data meta-analysis of the above RCTs in Malawi and Kenya

A single-stage individual participant-level meta-analysis was conducted using data of the aforementioned trials to compare the effect of ISTp-DHA-PPQ and IPTp-SP on birth outcome and the antenatal incidence and delivery prevalence of *P. falciparum* among all women with singleton births (13). Overall, 2866 women (paucigravidae=1697, multigravidae=1169) were included in the modified intention to treat (mITT) population (Kenya=1022, Malawi=1844). Compared with IPTp-SP, **ISTp-DHA-PPQ was associated with higher incidence of malaria parasitaemia during pregnancy** (47.4% versus 41.6%, IRR=1.14 [95% CI: 1.05–1.24], *P*=0.002) **and higher prevalence at delivery** (47.0% versus 39.1%, RR=1.20 [1.10–1.31], *P*<0.001) overall. **There were no differences in fetal loss** (2.6% versus 2.1%, RR=1.20 [0.73–1.97], *P*=0.46), **or early infant mortality by 6–8 weeks of age** (1.5% versus 1.7%, RR=0.88 [0.48–1.59], *P*=0.66). Results of this meta-analysis support the findings of the previously described single RCT, and indicate that in areas with near fixation of the quintuple dihydrofolate reductase (*dhfr*) and dihydropteroate synthase (*dhps*) mutant and low prevalence of the sextuple mutation, **ISTp-DHA-PPQ was inferior to IPTp-SP and may have resulted in more adverse birth outcomes**. The low sensitivity of currently available RDTs probably contributed to the poor performance of ISTp. These findings may not be generalizable to areas of higher parasite resistance.

Finally, modelling studies considering SP resistance across Africa, malaria transmission, accuracy of RDTs and SP effectiveness data in pregnancy have concluded that IPTp-SP is likely to remain superior to ISTp in areas where SP remains effective (14).

Key conclusions

- ISTp (either with SP or AL as treatment) was not inferior to IPTp-SP in preventing third trimester maternal anaemia, LBW and placental malaria in studies conducted in areas of low SP resistance in west Africa.
- The incidence of outpatient visits and malaria episodes during pregnancy was higher in the ISTp group compared to IPTp-SP.
- The results from the trials conducted in west Africa suggest that **IPTp-SP should be continued where SP resistance is low.**
- ISTp-DHA-PPQ was not superior to IPTp-SP in areas of high malaria transmission and high SP resistance of east and southern Africa and was associated with more malaria during pregnancy and at delivery in all gravidae and lower mean birth weight in paucigravidae.
- **IPTp-SP retains some of its effectiveness in areas of high SP resistance and should be continued in these areas.**

3.2 Acceptability of ISTp under trial conditions

The acceptability of ISTp both by providers (ANC health workers) and users (pregnant women) has been evaluated in three sub-Saharan countries within the RCT context.

In **Ghana**, overall, both ISTp and IPTp appeared equally acceptable to pregnant women as strategies for the control of MiP (*15*). The women were more concerned about quality of services received – in particular, the polite and patient attitude of health staff, and positive health implications for themselves and their babies – than about the nature of the intervention (15).

In **Malawi**, the user and provider acceptability study of ISTp-DHA-PPQ identified six areas of concern for health workers: blood tests, drugs, resources and stock, adherence to DHA-PPQ, communication and workload (16). For pregnant women the main issues identified were blood tests, drugs and reasons for repeat visits. Overall, both providers and users considered ISTp to be an acceptable alternative to IPTp.

Finally, in **Kenya**, ISTp-DHA-PPQ and IPTp-DHA-PPQ in the context of the study were generally acceptable among both users and providers, and were seen as potentially valuable alternatives to IPTp-SP (17). Among the several challenges identified, the most important was adherence to DHA-PPQ for the full course (3 days) among asymptomatic women in the routine setting.

Key conclusions

- Overall, **ISTp** (either with AQAS or DHA-PPQ) was considered to be an **acceptable alternative to IPTp-SP, both by providers and users in trial conditions**.
- Quality of care of ANC services as well as adherence to a 3-day course of treatment were concerns perceived by pregnant women and health workers, respectively.
- Further research would be needed to confirm these findings in larger studies, other settings and non-trial conditions.

3.3 Cost-effectiveness of ISTp

Based on the results of the aforementioned non-inferiority multicentre RCT evaluating ISTp with AL in HIV-negative women from four sub-Saharan countries in west Africa (Section 3.1.2), a CEA of ISTp was undertaken (11, 18).

Simulations were performed considering hypothetical cohorts of 1000 pregnant women receiving either ISTp-AL or IPTp-SP. Disability adjusted life years (DALYs) were calculated for LBW, severe or moderate anaemia, and clinical malaria. Cost estimates were obtained from data collected in observational studies, health facility costing studies and public procurement databases. The main outcome measure was the incremental cost per DALY averted.

The CEA found that delivering ISTp-AL to 1000 pregnant women averted –27.83 DALYs at an incremental cost of US$ 4929.00 (producing an incremental cost-effectiveness ratio [ICER] of US$ –177.10/DALY averted) and that **IPTp-SP averted more DALYs than ISTp-AL**.

In the probabilistic sensitivity analysis, the ICER was US$ –175.12/DALY averted. The CEA model presents the threshold below which the efficacy of IPTp-SP would have to fall for ISTp-AL to become a cost-effective option for the prevention of MiP at different levels of willingness to pay and insecticide-treated mosquito net (ITN) contribution (18). **Cost-effectiveness of ISTp-AL increased as the efficacy of IPTp-SP decreased**, though the level of IPTp-SP efficacy loss is sensitive to assumptions about the contribution of ITNs to malaria control, and the willingness-to-pay threshold used.

Taking these elements into consideration, the results indicate that at the current SP efficacy levels in the trial settings **it would not be cost-effective to switch from IPTp-SP to ISTp-AL.**

Areas of further research include the CEA of ISTp in areas of east Africa where SP resistance prevalence is high, and effects of malaria transmission on cost-effectiveness of the intervention.

Key conclusions

- **ISTp** (with AL) was found to be **more expensive and less effective** for prevention of MiP than IPTp-SP.
- **At the current levels of efficacy of IPTp-SP, it would not be cost-effective to switch from IPTp-SP to ISTp-AL.**

3.4 Effects of submicroscopic infections on maternal and infant outcomes

A longitudinal cohort study including 1037 pregnant women from Benin evaluated the effect of submicroscopic *P. falciparum* infections on maternal and infant outcomes (19). The study was conducted between 2008 and 2011, and enrolled pregnant women who were followed up monthly until delivery. At inclusion, polymerase chain reaction (PCR) and microscopy detected malaria parasites from peripheral blood in 40% and 16% of women, respectively. The proportion of infections declined markedly after two doses of IPTp-SP but rebounded to 34% (by PCR) at delivery. **Submicroscopic infections** during pregnancy **were associated with lower mean haemoglobin** irrespective of gravidity, and with increased **anaemia** risk in primigravidae (OR: 2.23; 95% CI: 0.98–5.07). Prospectively, submicroscopic infections at inclusion were associated with significantly increased risks of LBW in primigravidae (OR: 6.09; 95% CI: 1.16–31.95) **and premature births** in multigravidae (OR: 2.25; 95% CI: 1.13–4.46). In this study, parasitaemia occurred frequently during pregnancy, but routine microscopic and HRP2-detecting **RDTs failed to detect most episodes**.

Another longitudinal study conducted in Burkina Faso and Uganda analysed the correlation of PCR, microscopy and Pf/Pan combination RDTs performed on peripheral blood compared with results of malaria infection by placental histology (20). A total of 990 women were followed up to delivery between 2010 and 2012. Preliminary results indicate that **PCR had the higher detection rate** on peripheral blood than the other diagnostics. Using PCR as standard, all diagnostics typically had a higher sensitivity and lower specificity on samples from women experiencing fever symptoms, compared to those from women not experiencing fever symptoms. The variables of age, gravidity, presence of fever symptoms, prior treatment for malaria or IPTp and month of visit were all significant explanatory variables for predicting sensitivity, specificity, positive predictive value and negative predictive value, but the significance of each variable differed for the different statistics, diagnostics and country. **Country was a significant factor influencing the sensitivity and specificity of the different diagnostic tests** (sensitivity was always higher in Uganda than in Burkina Faso). **The prevalence of adverse birth outcomes** (including LBW, preterm delivery, stillbirths and miscarriage) **did not differ by parasite detection method used (RDT, microscopy or PCR) or by placental histology). However, maternal haemoglobin change between enrolment and delivery was influenced by the sensitivity of the parasite detection method used, gravidity and country.**

The sensitivity of the RDTs to detect malaria parasites in peripheral blood was also evaluated in pregnant women in the context of the ISTp RCT conducted in west Africa (11, 21). In Ghana, the sensitivity of the RDT declined progressively over the course of pregnancy from 89% (95% CI: 85–92%) at enrolment to 49% (95% CI: 31–66%) at delivery. Screening at first enrolment with an RDT detected 53% of all infections diagnosed during pregnancy. Seventy-five RDT negative infections were detected by PCR or microscopy in 540 women; these infections were not associated with maternal anaemia, placental malaria or LBW.

The sensitivity of RDTs in the pooled individual participant data meta-analysis of the two ISTp RCTs in Kenya and Malawi also showed that the highest prevalence of malaria was at enrolment, when 40.1% of women were infected, as measured by PCR (13). The sensitivity of RDTs during the enrolment visit was 64.8% (95% CI: 60.8–68.7%) compared to PCR and highest in paucigravidae women (74.8% [95% CI: 70.6–79.2%]) compared to multigravidae women (43.5% [95% CI: 36.4–50.7%]). At subsequent visits, the proportion of parasitaemic women decreased to 18.8% (95% CI: 17.5–20.1%), and the sensitivity of RDT to 33.8% (95% CI: 30.1–37.5%); 35.2% (95% CI: 30.4–39.9%) in paucigravidae women and 31.8% (95% CI: 26.1–37.5%) in multigravidae women.

Key conclusions

- **Submiscroscopic infections**, especially early in pregnancy, have been associated **with maternal anaemia, LBW and prematurity.**
- The effects of submicroscopic infections on adverse pregnancy outcomes need to be confirmed in large longitudinal studies and in different settings.
- **Malaria infection prevalence is highest at the antenatal booking visit** and declines thereafter. **The sensitivity of RDTs is also highest at the initial visit, in particular in primigravidae.** Thus, the use of RDTs to screen asymptomatic pregnant women for malaria infection is likely to be most beneficial at the first antenatal visit.

3.5 Impact of SP resistance and malaria transmission on IPTp-SP effectiveness

The **effectiveness of IPTp-SP is threatened by drug resistance** of the malaria parasites. SP resistance is due to the presence of mutant alleles in the *P. falciparum* genes encoding *dhfr* and *dhps*. The **triple *Pfdhfr* mutation N51I, C59R and S108N in combination with double *Pfdhps* mutant A437G and K540E – forming quintuple-mutant** haplotypes – has been associated with risk for treatment failure in malaria-infected children and non-pregnant adults who receive SP treatment (22). Moreover, quintuple mutants with an additional *dhps* mutation, **A581G**, have been associated with an even higher risk of SP failure (22, 23).

An initial report of the clinical impact of this A581G mutation was a retrospective cross-sectional study conducted between 2002 and 2005 among 104 delivering women in an area of the **United Republic of Tanzania**, where the fraction of parasites carrying the resistance allele at *dhps* codon 581 is relatively high (24). The study found an increased placental parasite density and inflammatory changes in women who reported taking IPTp-SP, but no effects on the prevalence of LBW was observed (24, 25).

A further study conducted in **Mozambique** during the same period (2003–2006) assessed the impact of IPTp and maternal HIV infection on the prevalence of molecular markers of SP resistance (26). *P. falciparum* isolates collected at delivery from women participating in a randomized, placebo-controlled trial of IPTp-SP were analysed. It was found that the prevalence of infections with parasites carrying quintuple resistance markers was 24% in the SP group and 12% in the placebo group. IPTp-SP increased the prevalence of molecular markers of resistance in the placenta (*P*=0.031), but not in peripheral blood and in HIV-infected women. However, **no association was found between infections with parasites carrying quintuple resistance markers and increased parasite density or malaria-related morbidity in mothers and children, nor on birth weight reduction.**

These findings are in accordance with those from a serial, cross-sectional analysis of the relationship between IPTp-SP use, SP-resistant *P. falciparum* and MiP morbidity during a period of 9 years at a single site in **Malawi** (1997–2006), which showed that, despite increasing SP resistance, MiP morbidity was not exacerbated (27). This study suggested that although IPTp-SP may contribute to the selection of quintuple mutant resistant parasites, **the use of IPTp-SP was not associated with increased parasite densities, greater placental inflammation or adverse delivery outcomes.**

A further cohort study conducted between 2008 and 2010 in the **United Republic of Tanzania** among 924 pregnant women analysed the effect of infecting parasite haplotypes on an infant's birthweight (22). Women received two doses of IPTp-SP. Quadruple-mutated or less-mutated haplotypes were mainly observed early during pregnancy, whereas quintuple-mutated and also 581G were encountered throughout pregnancy. Compared with infections with the less-mutated haplotypes, **infections with the sextuple haplotype mutation were associated with lower (–359 g) birthweights, although there was no association between SP use and lower birthweight.**

The effects of the presence of the sextuple mutant on IPTp-SP effectiveness have also been analysed in 1809 delivering women from **Malawi** between 2009 and 2011 (23). A total of 202 specimens were genotyped at codon 581 of *dhps*, 17 (8.4%) of whom harboured the sextuple mutant. **The presence of the 581G mutation was associated with higher risks of patent infection in peripheral blood** (adjusted prevalence ratio [aPR]: 2.76; 95% CI: 1.82–4.18) and placental blood (aPR: 3.28; 95% CI: 1.88–5.78) and higher parasite densities. Recent **SP use was not associated with increased parasite densities or placental pathology overall or with these outcomes among women with parasites carrying *dhps* A581G.**

A recent analysis of the geographical distribution of *P. falciparum* parasites carrying sextuple mutations indicates that the high prevalence (>30%) is maintained in the original areas where first identified in the United Republic of Tanzania, Kenya and Rwanda (28). Furthermore, detectable prevalence of sextuple mutants of below 10% seems to be increasingly detected in surrounding areas.

A systematic review and meta-analysis evaluated the impact of SP resistance on IPTp effectiveness (ter Kuile et al., unpublished). In vivo studies conducted between 2009 and 2011 on the efficacy of IPTp-SP in parasitaemic asymptomatic pregnant women from Burkina Faso, Kenya, Malawi, Mali and Zambia found that SP treatment failure and risk of reinfection were more frequent in areas with increasing resistance levels in parasite population (29). The meta-analysis using aggregated data from observational studies and trials conducted between 1997 and 2013 found that **IPTp effectiveness decreases with increasing SP resistance, but that even in areas with above 90% presence of quintuple mutations, IPTp-SP is associated with lower risk of LBW.** However, in areas of very high SP resistance (e.g. presence of >10% sextuple mutations) there was no more evidence that SP was associated with a lower risk of LBW or that the effectiveness of SP may be compromised in these limited areas.

Overall, results of these studies indicate the need for continued monitoring of SP resistance markers and further research into their impact on IPTp-SP effectiveness.

Very limited evidence was presented to the ERG on the possible impact of low transmission on the effectiveness of IPTP-SP. Recent modelling work (Walker et al, unpublished) estimated that at very low prevalence of malaria in primigravidae (e.g. ~5%), the number of cases of LBW prevented with IPTp-SP ranged from 1 to 7 per 1000 deliveries, at SP efficacies of 25% and 100%, respectively. The focus of the model on primigravidae was based on data derived from other studies, which estimated that primigravidae may have 20% additional risk of LBW due to malaria if not protected by IPTp or other preventive interventions. This work supports the current WHO position that it is not possible, based on current evidence, to establish a threshold level of malaria transmission below which IPTp-SP is no longer cost-effective.

Key conclusions

- **IPTp-SP remains effective** in preventing the adverse consequences of malaria on maternal and infant outcomes, including in areas where quintuple-mutant haplotypes *P. falciparum* mutations to SP are highly prevalent.
- The **association between *dhfr* 581G mutation and decreased LBW** in women receiving IPTp-SP compared to non-recipients of SP reported in limited areas from the United Republic of Tanzania has not been observed in other sub-Saharan countries and its potential impact on IPTp-SP effectiveness **requires further investigation**.
- **Further research on the impact of other SP resistance markers on IPTp-effectiveness should be done** in sub-Saharan countries where IPTp-SP is used.
- There is currently **no evidence of a threshold level of malaria transmission below which IPTp-SP is no longer cost-effective.**

3.6 Evaluation of DHA-PPQ for IPTp

Two studies have recently evaluated DHA-PPQ for IPTp in HIV-negative women. The results (unpublished) were presented and discussed at the meeting.

3.6.1 RCT comparing ISTp-DHA-PPQ, IPTp-DHA-PPQ and IPTp-SP in Kenya

This is the same study as the one reported for ISTp (see Section 3.1). The study was an **open-label three-arm RCT** conducted between 2012 and 2014 among **HIV-negative** pregnant women in an area of Kenya with high malaria transmission and SP resistance. The trial enrolled **1546** pregnant women of 16–32 weeks gestation who were randomized to receive either **ISTp-DHA-PPQ**, **IPTp-DHA-PPQ** or **IPTp-SP** three to four times during pregnancy at least 1 month apart. The primary outcome was malaria infection at delivery (composite of peripheral or placental parasitaemia detected by placental histology, microscopy or RDT). All participants received an LLN on enrolment.

The **prevalence of malaria infection at delivery was lower in the IPTp-DHA-PPQ than in the IPTp-SP arm**: 3.3% versus 10.2%; RR=0.32 (95% CI: 0.18–0.56); *P*<0.0001. There were no significant differences in adverse infant morbidity (composite of small for gestational age, LBW or preterm birth) between study arms; however, the mean birth weight was 87 g higher (95% CI: 24–150; *P*=0.01) in the IPTp-SP than in the IPTp-DHA-PPQ arm. **Stillbirths** (RR=0.25 [0.08–0.74]; *P*=0.01) **and infant mortality** by 6–8 weeks (RR=0.31 [0.10–0.94]; *P*=0.04) were **lower in the IPTp-DHA-PPQ arm** than in the IPTp-SP arm. The authors concluded that **DHA-PPQ is a potentially promising drug for IPTp.**

3.6.2 RCT comparing IPTp-DHA-PPQ with IPTp-SP in Uganda

This was a double-blind, three-arm RCT that compared three-dose **IPTp-SP** (starting at 20 weeks) with three-dose **IPTp-DHA-PPQ** (starting at 20 weeks) or **monthly DHA-PPQ** (starting as early as 16 weeks) in HIV-negative pregnant women from Uganda. Placebos of SP and DHA-PPQ were used, such that every 4 weeks women received the same number of tablets with the same appearance. The primary outcome was the prevalence of placental malaria based on the presence of any malaria parasites or pigment detected by histopathology. Electrocardiograms (ECGs) were performed to assess QTc intervals in 42 women just before their first daily dose of study drugs and 3–4 hours after their third daily dose of study drugs when they reached 28 weeks gestational age. A total of **300 HIV-negative women** were enrolled, 37% of whom were primigravidae, and 87% reported owning an LLN. At enrolment, 57% of women had malaria parasites detected by microscopy. The incidence of **symptomatic malaria was significantly higher in the SP arm** (41 episodes) compared to the three-dose IPTp-DHA-PPQ (12 episodes, *P*=0.001) or monthly DHA-PPQ (0 episodes, *P*<0.001) arms.

Maternal anaemia during pregnancy was significantly higher in the SP arm (34.9%) compared to the monthly DHA-PPQ arm (23.6%, *P*=0.04) but not to the three-dose DP arm (30.4%, *P*=0.43). The prevalence of any **placental malaria** by histopathology was significantly **higher in the SP arm** (50.0%) than in the three-dose IPTp-DHA-PPQ (34.1%, *P*=0.03) or monthly DHA-PPQ (27.1%, *P*=0.001) arms. There were no differences in individual birth outcomes between the treatment arms, but the risk of any adverse birth outcome was significantly lower in the monthly DHA-PPQ arm (9.2%) than in the three-dose DHA-PPQ arm (21.3%, *P*=0.02) and of borderline significance compared to the SP arm (18.6%, *P*=0.05). There were no significant differences in the incidence of any AEs apart from dysphagia, which was significantly higher in the monthly DHA-PPQ arm than in the three-dose DHA-PPQ arm (0.26 versus 0.04 episodes person year, *P*=0.02). Among 42 women who underwent ECG measurements at 28 weeks gestational age, all pre- and post-dosing QTc intervals were within normal limits (<450 msec) with no differences in the change in QTc intervals between study arms. Given the promising study results, **DHA-PPQ DP could be considered an alternative to SP** in areas with widespread antifolate resistance.

Key conclusions

- Recent studies evaluating **DHA-PPQ for IPTp** have found that the drug was **more efficacious than SP in reducing maternal malaria infection and anaemia at** delivery, **incidence of malaria** during pregnancy, **stillbirths** and infant mortality within 6–8 weeks.
- These **promising results** would need to be confirmed in a larger RCT involving women in areas with similar malaria transmission and SP resistance, and in areas with different malaria transmission and SP resistance levels.
- In addition, the **safety** of administering repeated doses **of DHA-PPQ** (with specific attention to QTc prolongation) requires **further investigation**, as well as adherence to the required 3-day regimen for each DHA-PPQ treatment dose and the safety of DHA-PPQ co-administration with antiretroviral therapy in HIV-infected women.

3.7 Embryotoxicity of artemisinin derivatives in animal studies

Extensive new information about the embryotoxicity of artemisinins has been gathered since the last WHO assessment of artemisinin safety in 2006. The embryotoxic effects, which include embryolethality, malformations and decreased fetal weight, have been further characterized (30-34). Moreover, the embryotoxic effects previously seen primarily with artesunate have now been observed with other artemisinin derivatives (including artemether, arteether, DHA, artemisone and artelinic acid), indicating a general class effect on multiple species of animals, namely rats, rabbits and monkeys (35-39).

A study conducted in pregnant monkeys also found significant embryotoxic effects after 12 days of treatment, when treatment was started on day 20 post conception (pc) (39). The **induction of embryolethality** by artesunate has thus been reported so far **in three species (rat, rabbit and monkey).**

Embryotoxic effects are dose and time dependent. The most sensitive embryonic period is when the primitive erythroblasts, derived from the visceral yolk sac, are predominant in the circulation (40, 41). In rats, this has been established as between **days 10 and 14 pc**, which corresponds developmentally in humans to weeks **4–10 pc (or 6–12 post last menstrual period [LMP]) in human pregnancy**.

The explanation for the apparently lesser sensitivity to artemisinins in human pregnancy has not been determined and needs further investigation. Other gaps in knowledge in animal studies include the mechanisms of embryotoxicity and of erythropoiesis.

Key conclusions

- **Embryo deaths and malformations induced by artemisinin** derivatives have been reported in **rats, rabbits and monkeys**. The effects are dose and time dependent.
- By extrapolation of animal toxicity findings it is possible to estimate in humans a putative sensitive embryonic period between the start of week 4 to the end of week 10 pc, or from the start of week 6 to the end of week 12 post LMP.

3.8 Safety of artemisinin exposure in the first trimester of pregnancy

Data on the safety of artemisinin exposure in the first trimester of pregnancy in the Myanmar–Thai border and sub-Saharan Africa has been gathered and analysed to determine the risk for the development of the fetus.

3.8.1 Retrospective analysis of ANC records of the Shoklo Malaria Research Unit, Thailand

From 1986 to 2010, a total of 773 women were treated for malaria in the first trimester of pregnancy, **64** of them with artemisinin derivatives (42). Single-course treatments were with chloroquine (354), quinine (355) or artesunate (64). Intentional treatment with artemisinins was predominantly monotherapy (21 of 30 women) whereas inadvertent treatment (34 women) was with an ACT in all cases. Among the 34 women inadvertently given an ACT, eight (24%) miscarried. The **risk of miscarriage was similar for women treated with chloroquine** (92 [26%] of 354), **quinine** (95 [27%]) of 355), **or artesunate** (20 [31%] of 64; *P*=0.71) in the first trimester of pregnancy. **Drug exposures between 6 and 12 weeks of gestation** (putative embryonic period of sensitivity) were investigated further: **miscarriage proportions were 40%** (10 of 25) **for women treated with artesunate compared with 26%** (51 of 193; *P*=0.162) **for quinine and 30%** (64 of 215; *P*=0.360) **for chloroquine** (42). Exposure to antimalarial therapies was not randomized, and women with perceived worse prognosis were more like to be given artesunate. Allowing for a plus or minus 14-day error on estimation of gestational age and so broadening the exposure window to between 4 weeks and less than 14 weeks, the miscarriage proportions were 34% (17 of 50) for women who received artesunate compared with 26% (83 of 323; *P*=0.232) for quinine and 26% (87 of 329; *P*=0.307) for chloroquine. No significant excess of congenital malformations was reported in women contributing to this analysis. Malaria episodes in the first trimester of pregnancy were associated with increased risk of miscarriage. Preliminary results of a further analysis of the ANC records from the Shoklo Malaria Research Unit, including **171 exposures to artesunate** in the first trimester of pregnancy between 1994 and 2013, also indicate that there may be no increased risk of miscarriage or congenital abnormalities associated with artemisinin exposure compared with quinine exposure.

3.8.2 Prospective observational studies in sub-Saharan Africa

Data from six prospective cohort studies conducted in Burkino Faso, Kenya, Mozambique, Rwanda, United Republic of Tanzania and Zambia between 2004 and 2013 have been pooled and analysed (43). The number of pregnancies included in the analysis depended on the outcome: 5520 for miscarriage (restricted to women enrolled before 28 weeks gestation and including loss to follow-up until last visit date), 6909 for stillbirths and 6583 for congenital malformations (restricted to live-births and stillbirths). Of the 5520 pregnancies included in the miscarriage analysis, **526 (9.5%) had a confirmed ACT exposure in the first trimester** and 384 (7.0%) of these were in the putative embryo-sensitive period. Another 106 (1.9%) were exposed to quinine anytime in the first trimester and 55 (1.0%) in the putative embryo-sensitive period for artemisinins. The unexposed comparison group included 4888 (88.6%) pregnancies with no indication of malaria or antimalarial treatment in the first 18 weeks of pregnancy.

Pregnancies with a confirmed **ACT exposure in the first trimester were at a significantly lower risk of miscarriage compared to those with a confirmed quinine exposure** (adjusted hazard ratio [HR] 0.40 [0.20–0.82], *P*=0.012). The sensitivity analysis assessing **the effect of ACT exposures in the artemisinin putative embryo-sensitive period showed similar risk of miscarriage among artemisinin and quinine exposed pregnancies** (adjusted HR 0.80 [0.43–1.51], *P*=0.514). There was **no difference in the risk of stillbirth for pregnancies exposed to ACT in the first trimester compared to those unexposed to antimalarial or exposed to quinine in the same period** (adjusted HRs: 0.71 [0.38–1.32] and 0.81 [0.22–2.95], respectively). **The risk of**

stillbirth for exposures restricted to the putative embryo-sensitive period was slightly higher than in the overall first trimester. In this 6–12 weeks gestation period, the effect estimates suggest pregnancies exposed to artemisinin were at higher risk of stillbirth than the quinine exposed comparison, but event numbers were few and this was not statistically significant (adjusted HR: 1.69 [0.62–4.63]).

3.8.3 Aggregated meta-analysis Africa and Myanmar–Thai border

An aggregated meta-analysis that combined the pooled effect estimates from the African analysis with the effect estimates from the Myanmar–Thai border showed a similar lower risk of miscarriage for pregnancies exposed to an artemisinin derivative at any time in the first trimester compared to those exposed to quinine in the same period (summary adjusted HR=0.45 [0.27, 0.75], I^2=0%) and no difference for exposures restricted to the putative embryo-sensitive period (HR=0.93 [0.55, 1.55], I^2=39%) (43). A total of 604 (526 + 78) pregnancies with confirmed artemisinin exposure in the first trimester of pregnancy contributed to this aggregated meta-analysis. Overall, there were 0.67% (155/23 198) cases of major congenital malformation. The prevalence of major congenital malformations was similar among first-trimester artemisinin and quinine exposures (artemisinins=0.58% [3/519]; quinine=0.72% [3/416], prevalence difference=0.002 [–0.015–0.019], I^2=0%, P=0.846).

Overall, these findings suggest that artemisinin-based treatment used for malaria treatment in the first trimester are associated with a lower risk of miscarriage than quinine treatment. However, the analysis has some limitations because it cannot account for potential confounding by indication, given that the data on malaria diagnosis, parasitaemia or severity of symptoms were not available across all African sites and there was limited power to assess congenital malformations (43). Adherence to malaria treatment (7 days oral quinine versus 3 days oral ACT, for uncomplicated malaria) may also be influencing the observed results. Nevertheless, results obtained in Africa and in Thailand (where these data were available and where most treatments were supervised) were consistent. Finally, these studies were not designed to assess fetal cardiovascular effects.

The **artemisinin exposures from the African analysis were predominantly AL** (95% [532/560], and the remaining 40 were AQAS, all from Burkina Faso), whereas artemisinin exposures from the Myanmar–Thai border included a wide range of treatments (MQ-AS, AL, artesunate plus clindamycin, artesunate monotherapy and DHA).

3.8.4 WHO pilot pregnancy registry project

The WHO pilot pregnancy registry project conducted in Ghana, Kenya, Uganda and United Republic of Tanzania has so far captured information on 24 pregnancies exposed to artemisinin derivatives in the first trimester of pregnancy. Thirteen of these pregnancies had confirmed exposures during 6–12 weeks post LMP (the estimated embryo-sensitive period). The preliminary results of the registry indicate that no adverse effects were observed in those pregnancies exposed to artemisinin.

3.8.5 Post-ERG meeting updated analyses

ERG recommended to the groups working on artemisinin exposures in the first trimester of pregnancy that they perform additional analyses presenting the number of pregnancies with known birth outcomes and confirm drug exposure by each study and antimalarial. The analysis has been performed and included in Annex 2.

Key conclusions

- Updated evidence on the safety of artemisinin indicates that **ACT exposure in the first trimester of pregnancy does not increase the risk of miscarriage, stillbirths or major congenital malformations compared to quinine.**
- Women treated with an artemisinin at any time during the first trimester of pregnancy were at similar or lower risk of miscarriages than those treated with oral quinine.
- Based on the available updated evidence, the first-line treatment of uncomplicated malaria in the first trimester of pregnancy could be revised to include ACTs as a therapeutic option.
- Most of the data of artemisinin exposure in the first trimester of pregnancy are from AL exposure; consequently, more safety data are needed with other ACTs.
- There is a need for **continued monitoring and pharmacovigilance of drug exposure in early pregnancy, including more information on congenital malformations.**

3.9 Efficacy and safety of ACTs for malaria treatment in the second and third trimester of pregnancy

A recent study and new meta-analysis on the efficacy and safety of ACTs for treatment of uncomplicated malaria in the second and third trimester of pregnancy were presented at the meeting.

3.9.1 RCT in Africa

A multicentre non-inferiority open-label RCT evaluating the efficacy and safety of four ACTs for the treatment of uncomplicated malaria in the second and third trimester of pregnancy was conducted between 2010 and 2013 in Burkina Faso, Ghana, Malawi and Zambia. The trial included **3428 HIV-negative pregnant women** with detectable falciparum parasitaemia (any density and regardless of symptoms) **treated with either AL, AQAS, mefloquine-artesunate (MQAS) or DHA-PPQ**. The primary endpoints of the study were the PCR-adjusted cure rates at day 63 and for safety outcomes. The PCR-adjusted cure rates were 94.8% for AL, 98.5% for AQAS, 99.2% for DHA-PPQ and 96.8% for MQAS. There was no significant difference between AQAS, DHA-PPQ and MQAS.

The cure rate for AL was significantly lower, although the difference was within the 5% non-inferiority margin. The unadjusted cure rates were significantly lower for AL (52.5%) than for AQAS (82.3%), DHA-PPQ (86.9%) and MQAS (73.8%). No significant difference in serious AEs or birth outcomes was found between treatment arms. **Drug-related AEs** such as asthenia, poor appetite, dizziness, nausea, and vomiting **were significantly more frequent in the MQAS (50.6%) and** AQAS **(48.5%) than in the DHA-PPQ (20.6%) and AL (11.5%) arms (*P*<0.001).** AL had the best tolerability profile and acceptable cure rates, but the shortest post-treatment prophylaxis. Based on efficacy and safety, DHA-PPQ seems the most suitable treatment for uncomplicated malaria and for ensuring long post-treatment prophylaxis.

3.9.2 Meta-analysis of the safety of artemisinin derivatives for treatment of MiP

A systematic review and meta-analysis has evaluated the risk of adverse pregnancy outcomes associated with use of artemisinins during the second and third trimester of pregnancy compared to use of other or no antimalarial therapies (44). The meta-analysis was performed using data of 23 studies (14 cohort studies and 9 RCTs) to generate pooled odds ratios (POR) for

miscarriage, stillbirth, any fetal loss, and congenital anomalies using Mantel-Haenszel fixed effects model using a 0.5 continuity correction for zero cells.

Second-trimester artemisinin exposures were not associated with an increased risk of miscarriage compared to community controls (POR=1.13 [95% CI: 0.77–1.66], I^2=86.7%, 3 studies). Second or third-trimester artemisinin exposure was associated with **similar odds of congenital anomalies** (POR=1.00 [95% CI: 0.27–3.75], I^2=0%, 3 studies) **and lower odds for stillbirth** compared to quinine (POR=0.49 [95% CI: 0.24–0.97], I^2=0%, 3 studies). These findings suggest that use of artemisinins in the second and third trimester does not increase the risk of miscarriage, stillbirth or congenital anomalies compared to quinine.

3.9.3 Meta-analysis of the efficacy and tolerability of ACTs versus oral quinine in the treatment of clinical malaria in the second and third trimester of pregnancy in Africa

A meta-analysis of RCT data to compare the efficacy, safety and tolerability of ACTs versus quinine and other non-ACT antimalarial medicines in the second and third trimester was recently performed (45). Of 372 screened studies, six trials involving 807 pregnancies were included. The median PCR-adjusted failure rate by days 28 to 63 in the non-ACT group was 6 (range 0–37) per 100 women, and lower (not significant) in the ACT group overall (pooled risk ratio [PRR] 0.41 [95% CI: 0.16–1.05], I^2=38%, 6 studies). Subgroup analysis showed effect modification by comparator drug; ACTs were significantly more effective when compared to oral quinine (PRR 0.20 [95% CI: 0.08–0.49], I^2=0%, 4 studies), but not when compared to other non-ACTs (PRR 1.17 [95% CI: 0.35–3.92], I^2=0%, 2 studies). The median birth weight in the non-ACT group was 2887 g (range 2785–3012 g) and on average 75 g higher in the ACT group (95% CI: 3–148, I^2=6%, 6 studies). There were no differences in the risk of fetal death (PRR 1.04, 0.49–2.20, I^2=0%, 6 studies) and congenital abnormalities (PRR 1.38 [0.31–6.08], I^2=0%, 6 studies). ACTs were better tolerated than quinine and associated with less tinnitus (PRR 0.19 [0.03–1.11], I^2=97%, 4 studies), dizziness (PRR 0.64 [95% CI: 0.44–0.93], I^2=46%, 3 studies) and vomiting (PRR 0.33 [95% CI: 0.15–0.73], I^2=65%, 3 studies). Study limitations included limited number of trials, and high heterogeneity of included trials with regards to ACTs used, outcomes measured and differences in malaria endemicity. These results suggest that ACTs are more efficacious, better tolerated and easier to administer than oral quinine for the case management of malaria in the second and third trimester of pregnancy.

Key conclusions

- Data on **ACT use for treatment of clinical uncomplicated malaria** in the second and third trimester of pregnancy indicate that they are **safe in terms of pregnancy outcomes and efficacious** to clear *Plasmodium* parasites (especially DHA-PPQ).
- ACTs can thus be considered a safe and efficacious option for treatment of clinical uncomplicated malaria in women in the second and third trimester of pregnancy.

3.10 General considerations on use of antimalarial medicines in pregnancy

3.10.1 Regulatory processes for recommendation of medicines for use in pregnancy

The European regulatory guidelines for labelling of medicines use in pregnancy were presented. The European Medicines Agency has adopted benchmarking procedures to estimate the embryotoxic risk of drugs in pregnancy. Threshold are used that depend on the number of pregnancies exposed to the medicinal product with known safe pregnancy outcomes. Thus, if no

increase in the global incidence of major malformations has been observed among at least **300 first-trimester prospectively collected drug-exposed pregnancies with known pregnancy outcomes (births or fetopathological examinations),** then the drug would not be responsible for a 10-fold or more increase in the overall incidence of malformations. Similarly, if no increase in the global incidence of major malformations has been observed among at least **1000** first-trimester-exposed prospectively collected pregnancies with known pregnancy outcomes (births or fetopathological examinations), then the drug would not be responsible for a twofold or more increase in the overall incidence of malformations.

3.10.2 WHO experience

In 2012, WHO recommended the use of efavirenz as first-line treatment of HIV infection in pregnancy despite pre-clinical data showing embryotoxicity, based on comprehensive reviews of safety data on pregnant women and programmatic superiority to standard of care (46). A similar approach could be followed to support an updated WHO recommendation of ACT use in the first trimester of pregnancy.

3.11 Report of increased mother-to-child transmission of HIV following IPTp-MQ

The efficacy and safety of MQ have recently been evaluated in two multicentre RCTs for IPTp in five sub-Saharan countries conducted between 2009 and 2013 (47, 48). Results of the trial in HIV-negative women concluded that despite MQ having a better antimalarial prophylactic effect, its tolerability was worse than that of SP, which limited its potential for IPTp in HIV-negative women. The trial in HIV-positive women was designed as a **double-blind placebo-controlled trial that enrolled 1071** participants from Kenya, Mozambique and United Republic of Tanzania (47).

IPTp-MQ was associated with significant reduction in maternal parasitaemia (RR=0.47 [95% CI: 0.27–0.82], *P*=0.008), and placental infection (RR=0.52 [95% CI: 0.29–0.90], *P*=0.021), and reduced incidence of non-obstetric hospital admissions (RR=0.59 [95% CI: 0.37; 0.95], *P*=0.031). There were no differences in the prevalence of adverse pregnancy outcomes between groups. However, drug tolerability was poorer in the MQ group than in the control group (29.6% referred dizziness and 23.9% vomiting after the first IPTp-MQ administration) and HIV viral load at delivery was higher in the MQ group than in the control group (*P*=0.048). The frequency of perinatal **mother-to-child transmission of HIV was increased in women who received MQ** (RR=1.95 [95% CI: 1.14–3.33], *P*=0.015) in an exploratory analysis. This finding needs further studies on the possible mechanisms underlying the twofold increased risk of mother-to-child transmission of HIV associated to three-dose IPTp-MQ. It is also important to understand the **implications of co-administration of antimalarials and antiretroviral therapies** before recommending new antimalarial drugs in HIV-infected individuals.

Key conclusions

- More **studies in HIV-infected pregnant women** are needed, including evaluation of **mother to child transmission and drug interactions** between antimalarial medicines and antiretroviral therapies.

4 General conclusions and recommendations

4.1 Malaria prevention in pregnancy

IPTp-SP remains effective and highly cost-effective in preventing the adverse consequences of malaria on maternal and fetal outcomes, including in areas where quintuple-mutant haplotypes of *P. falciparum* to SP (namely, the triple *Pfdhfr* mutation N51I, C59R and S108N in combination with double *Pfdhps* mutant A437G and K540E) are highly prevalent. IPTp-SP should thus be aggressively scaled up in line with the current WHO recommendations.

In areas of very high SP resistance (defined by high prevalence of *P. falciparum* sextuple SP mutations, including A581G *Pfdhps*), IPTp-SP should be continued as recommended. The association between sextuple parasite mutations and decreased LBW reported in limited areas from the United Republic of Tanzania has not been observed in other sub-Saharan countries where the *Pfdhps* A581G is present, and its potential impact on IPTp-SP effectiveness requires further investigation. In these limited areas, additional measures to prevent malaria in pregnant women could be considered, such as screening and treatment at the first ANC visit, given the higher sensitivity of RDTs in the first ANC visit. The benefits and cost-effectiveness of adding single screening and treatment at the first ANC visit to IPTp-SP should be evaluated in pilot studies.

In areas where IPTp-SP is implemented and transmission has been reduced to very low levels as a result of successful control strategies, IPTp-SP should be continued. There is currently no evidence of a threshold level of malaria transmission below which IPTp-SP is no longer cost-effective and should be discontinued. WHO recommends the continuous implementation of IPTp-SP until countries have reached very low transmission and are targeted for elimination by the national malaria programme.

Recent studies have evaluated ISTp at ANC as an alternative to IPTp-SP. In this strategy, women are screened for malaria with an RDT at each ANC visit and only women who test positive are treated. This strategy resulted in a higher proportion of maternal infections and clinical malaria during pregnancy compared to IPTp-SP, although it was non-inferior in terms of the proportion of LBW infants. In addition, ISTp was found to be less cost-effective than IPTp-SP. Thus, the evidence reviewed does not support a recommendation for IST as an alternative to IPTp-SP.

Recent studies of IPTp-DHA-PPQ found that DHA-PPQ was not associated with improved birth weight compared to IPTp-SP. However, it was more efficacious than SP in reducing maternal and placental malaria infection and anaemia at delivery, incidence of malaria infection and clinical episodes during pregnancy, stillbirths and infant mortality within 6–8 weeks. To confirm the potential of DHA-PPQ for IPTp, larger RCTs are needed with prevalence of LBW as the primary outcomes. In addition, the safety of administering repeated doses of DHA-PPQ (with specific attention to QTc prolongation) requires further investigation as well as adherence to the required 3-day regimen for each DHA-PPQ treatment dose.

4.2 Malaria treatment in pregnancy

The recommended use of quinine plus clindamycin for treatment of uncomplicated malaria episodes in the first trimester of pregnancy was based on safety risk assessment of ACT exposure in early pregnancy, largely based on pre-clinical observations. A more complete risk–benefit assessment that takes into account recent safety data on ACT exposure in the first trimester of pregnancy together with the ease of use and acceptability of administration of ACTs (compared with a 7-day course of quinine plus clindamycin given three times daily) justify the inclusion of ACTs as a potential treatment option.

New evidence from 1025 pregnancies with confirmed artemisinin exposure in the first trimester indicates that artemisinin does not increase the risk of miscarriage, stillbirths or major congenital malformations. Most of the available data reviewed derive from AL exposure (544 pregnant women with confirmed exposure in the first trimester). The comparison of carefully documented safety data on 604 women exposed to only ACTs compared to 595 exposed to only quinine in the first trimester of pregnancy showed that ACT exposure was associated with a significantly reduced rate of miscarriage compared to quinine. Therefore, if available, AL should be considered as the preferred ACT treatment option in the first trimester.

The WHO recommendations for first trimester pregnancy treatment of clinical uncomplicated malaria episodes should be updated as follows: **"Treat pregnant women with uncomplicated *P. falciparum* malaria with either the first-line ACT for three days or quinine and clindamycin for seven days."** AL should be the preferred ACT to be administered. Importantly, AS-SP should not be administered in the first trimester of pregnancy and quinine should always be administered with clindamycin and never alone.

Although the evidence regarding the safety of ACTs in early pregnancy has been strengthened by the review of the recent data, there is the need for continued monitoring of drug safety, birth outcomes and neonatal mortality. In the light of the evidence from an RCT suggesting a possible increased risk of mother-to to-child transmission of HIV associated with IPTp-MQ, more studies in HIV-infected pregnant women are needed, including evaluation of mother-to-child transmission and interactions between antimalarial medicines and antiretroviral therapies.

The WHO recommendation of efavirenz (EFZ) as first-line treatment of HIV infection in pregnancy despite pre-clinical data showing congenital malformations was based on comprehensive reviews of safety data on pregnant women and programmatic advantages compared to standard of care. The assessment was summarized in a WHO publication laying out the rationale for public health use, and then included in the WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. A similar approach could be used by WHO to support the new recommendation of ACT use in the first trimester of pregnancy.

Annex 1 Meeting pre-reads

Publication	Country and study years	Study description and main conclusions
Alifrangis et al. (49)	Uganda, United Republic of Tanzania and Ethiopia 2004–08	Molecular study on the evolutionary origin of the A581G mutation by characterizing microsatellite diversity flanking *Pfdhps* triple-mutant alleles and comparing it with double-mutant alleles from the same areas.
Almond et al. Unpublished (7)	Malawi 2011	Provider and user acceptability study of intermittent screening and treatment in pregnancy (ISTp) with dihydroartemisinin-piperaquine (DHA-PPQ) in Malawi. Although obstacles to the successful implementation of ISTp-DHA-PPQ were acknowledged by health workers and pregnant women, overall both groups consider ISTp an acceptable alternative to intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP).
Awine et al. Unpublished (50)	Ghana 2011–13	Follow-up study on the risk of malaria in infants born to women managed in pregnancy with ISTp for malaria or IPTp-SP (randomized controlled trial, RCT). No differences on infants' malaria incidence were found between groups.
Burger et al. Unpublished (45)	Malawi, United Republic of Tanzania, Uganda and Thailand 1995–2009	Meta-analysis of the efficacy and safety of artemisinin-based combination therapies (ACTs) versus quinine for uncomplicated malaria in the second and third trimester of pregnancy. Results suggest that 3-day ACT regimens are more effective and better tolerated than 7 days of oral quinine.
Cottrell et al. (19)	Benin 2008–11	Cohort study of 1037 pregnant women that evaluated the impact of submicroscopic infections on pregnancy outcomes. Submicroscopic infections were associated with lower mean haemoglobin, increased risk of low birth weight (LBW) in primigravidae and premature births in multigravidae.
D'Allesandro et al. Unpublished (51)	Burkina Faso, Ghana, Malawi and Zambia 2010–13	Open-label, non-inferiority, multicentre RCT evaluating four ACTs for the treatment of uncomplicated malaria in the second and third trimester of pregnancy. A total of 3428 pregnant women were treated with either artemether-lumefantrine (AL), amodiaquine-artesunate (AQAS), mefloquine-artesunate (MQAS) or DHA-PPQ. AL had the best tolerability profile and acceptable cure rates, but the shortest post-treatment prophylaxis. DHA-PPQ seemed to be the most suitable treatment.
Dellicour et al. Unpublished (43)	Zambia, United Republic of Tanzania, Rwanda, Kenya, Mozambique, Burkina Faso and Thailand 1986–2014	Meta-analysis on the safety of artemisinin exposure in the first trimester of pregnancy, on pregnancy outcomes. A total of 7127 pregnancies from six sub-Saharan African countries and 21 659 from Thailand contributed to the analyses. Compared to oral quinine no increased risk of miscarriage or stillbirth was observed following artemisinin treatment for uncomplicated malaria in the first trimester of pregnancy.

Publication	Country and study years	Study description and main conclusions
Desai et al. Unpublished	Kenya 2012–14	Open-label three-arm superiority RCT evaluating the efficacy and safety of ISTp-DHA-PPQ, compared with IPTp-SP and IPTp-DHA-PPQ. A total of 1546 HIV-negative women were enrolled. ISTp-DHA-PPQ was not superior to the IPTp-SP strategy, and was associated with a higher incidence of malaria infection and clinical malaria during pregnancy than IPTp-SP. IPTp-DHA-PPQ reduced the risk of anaemia and malaria infection at deliver, the incidence of clinical malaria during pregnancy, and the risk of stillbirths and early infant mortality.
European Medicines Agency (EMeA)	2009	Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling.
Fernandes et al. Unpublished (18)	Gambia, Mali, Burkina Faso and Ghana 2010–12	Study on the incremental cost and cost-effectiveness of ISTp with AL compared to IPTp-SP (RCT). Results indicate that currently switching from IPTp-SP to ISTp-AL will not be cost-effective.
González et al. (47)	Kenya, Mozambique and United Republic of Tanzania 2010–13	Double-blind, placebo-controlled RCT evaluating the efficacy and safety of IPTp with mefloquine (MQ) in 1071 HIV-infected women on daily contrimoxazole (CTX) prophylaxis. IPTp-MQ + CTX was more efficacious than CTX alone for prevention of maternal parasitaemia and anaemia at delivery. The incidence of hospital admissions in pregnancy was also reduced in MQ recipients. However, MQ was poorly tolerated and found to be associated with an increased risk of mother-to-child transmission of HIV in an exploratory analysis.
González et al. Unpublished (40)	2015	Review on artemisinin derivatives embryotoxicity in animal studies. Embryotoxic effects have been reported in rats, monkeys and rabbits. Effects are dose and time dependent. The estimated period of sensitivity in humans is from the start of week 4 to the end of week 10 post conception.
Gutman et al. (23)	Malawi 2009–11	Observational study of delivering women that evaluated IPTp-SP effectiveness and the effect of sextuple mutations (quintuple + A581G) on parasitological and pregnancy outcomes. The results suggest that IPTp-SP failed to inhibit parasite growth but did not exacerbate pathology among women infected with sextuple-mutant parasites.
Gutman et al. Unpublished (13)	Malawi and Kenya 2011–14	Individual pooled analysis of RCT data from Malawi and Kenya comparing ISTp-DHA-PPQ with IPTp-SP. ISTp-DHA-PPQ was associated with higher risk of malaria parasitaemia during pregnancy.
Gutman et al. Unpublished (52)	2015	Systematic review and meta-analysis of the efficacy and safety of repeated doses of DHA-PPQ for treatment and prevention of malaria in children and adults. The limited data on repeat DHA-PPQ exposures suggest that repeat 3-day courses of the drug given at monthly intervals may be safe and effective and a good option for IPTp.
Harrington et al. (24)	United Republic of Tanzania 2002–05	Molecular analysis of placental blood samples from 87 delivering women that found an increase of mean parasite density of placental parasitaemia in samples from women reporting IPTp use.

Publication	Country and study years	Study description and main conclusions
Hill et al. Unpublished (17)	Kenya 2013–14	User and provider acceptability study of ISTp-DHA-PPQ and IPTp-DHA-PPQ. Within a trial context, both strategies were generally acceptable among both users and providers. The most important challenge identified was concerns with adherence to DHA-PPQ in the routine setting, requiring further studies.
Hopkins et al. Unpublished (20)	Burkina Faso and Uganda 2010–12	Cohort study of pregnant women enrolled at the antenatal care (ANC) clinic to evaluate rapid diagnostic tests (RDTs) performance for screening of malaria in pregnancy (MiP) and its association with placental infection and birth outcomes.
Kakuru et al. Unpublished (53)	Uganda 2014–15	Double-blind, three-arm RCT comparing the efficacy and safety of three-dose IPTp-DHA-PPQ, with three-dose IPTp-SP and monthly DHA-PPQ in 300 HIV-negative women. The prevalence of any placental malaria by histopathology was significantly higher in the SP arm (50.0%) compared to the three-dose DHA-PPQ (34.1%, *P*=0.03) or monthly DHA-PPQ (27.1%, *P*=0.001) arms. Compared to three-dose SP, three-dose DHA-PPQ and monthly DHA-PPQ were equally safe and well tolerated and significantly reduced the incidence of symptomatic malaria and prevalence of parasitaemia during pregnancy.
Kovacs et al. Unpublished (44)	2015	Systematic review and meta-analysis of the risk of adverse pregnancy outcomes associated with use of artemisinins during the second and third trimester of pregnancy compared to use of other or no antimalarial therapies. Data suggest that use of artemisinins in the second and third trimester does not increase the risk of miscarriage, stillbirth or congenital anomalies compared to quinine.
Lagarde et al. (54)	Ghana 2009	Study on the potential barriers of ISTp implementation by ANC providers. Findings suggest that resistance to policy change would be low and would disappear if maternal and infant health outcomes were improved by the new strategy.
Madanitsa et al. Unpublished (12)	Malawi 2011–13	Open-label two-arm RCT comparing ISTp-DHA-PPQ and IPTp-SP. The prevalence of adverse birth outcome was similar in both arms. The prevalence of malaria at delivery was higher in the ISTp-DHA-PPQ arm (48.7% versus 40.8%): RD=7.85 (3.07–12.63); RR=1.19 (1.07–1.33), *P*=0.007 (paucigravidae: RR=1.16 [1.04–1.31], *P*=0.011; multigravidae: RR=1.29 [1.02–1.63], *P*=0.037). Fetal loss was more common with ISTp-DHA-PPQ (2.6% versus 1.3%; RR=2.06 [1.01–4.21], *P*=0.046) and highest among non-DHA-PPQ-recipients (3.1%) in the ISTp-DHA-PPQ arm.
McGready et al. (42)	Thailand 1986–2010	Analysis of antenatal records of women in the first trimester of pregnancy attending Shoklo Malaria Research Unit ANC clinics. Data indicate that a single episode of *falciparum* or *vivax* malaria in the first trimester of pregnancy can cause miscarriage. The risk of miscarriage was similar for women treated with chloroquine (92 [26%] of 354), quinine (95 [27%] of 355), or artesunate (20 [31%] of 64; *P*=0.71).
Menendez et al. (26)	Mozambique 2003–05	Molecular analysis of samples from peripheral and placental blood of 1030 delivering women participating in an RCT of IPTp-SP versus placebo. It showed an increase in resistance markers prevalence in the IPTp-SP group in the placenta and in HIV-infected women. This effect did not translate into severe infections or adverse clinical outcomes.

Publication	Country and study years	Study description and main conclusions
Minja et al. (22)	United Republic of Tanzania 2008–10	Cohort study of 924 pregnant women analysing the effect of infecting parasite haplotypes on birthweight. Compared with infections with the less-mutated haplotypes, infections with the sextuple haplotype mutation were associated with lower (359 g) birthweights.
Pell et al. (55)	Ghana 2010	Study on the attitudes and behaviours of pregnant women related to ISTp and IPTp under trial conditions. Despite the discomfort of the finger-prick required to perform ISTp, trial participants generally expressed more positive sentiments towards IST-AL than IPTp-SP. Nonetheless, questions remain about adherence to a multiple-dose antimalarial regimen during pregnancy.
Medicines for Malaria Venture (MMV)	2013	Confidential report of the MMV–Pregnancy Strategic Advisory Board, London, 4 Nov. 2013.
Tagbor et al. (10)	Ghana 2007–08	Non-inferiority, open-label RCT comparing ISTp-SP, ISTp-AQ-AS and IPTp-SP in 3333 women. ISTp was not inferior to IPTp-SP in preventing severe maternal anaemia at the third trimester of pregnancy and LBW. No information on placental infection was available. The results suggested that IST could be an alternative strategy to IPTp-SP in some areas and concluded that further investigations were required to confirm the study results in other settings.
Tagbor et al. Unpublished (11)	Gambia, Mali, Burkina Faso and Ghana 2010–12	Non-inferiority, open-label multicentre RCT comparing ISTp-AL with IPTp-SP in 5354 HIV-negative pregnant women from four west African countries with low prevalence of SP resistance. IST was found to be not inferior to IPTp-SP in preventing maternal anaemia, LBW and placental infection. However, the incidence of malaria episodes during pregnancy was increased in the IST group compared with the IPTp one.
Taylor et al. (56)	Malawi 1997–2005 & 2010, Democratic Republic of the Congo 2007 and United Republic of Tanzania 2002–05	Analysis of SP mutants haplotypes and emerging lineage of *P. falciparum* parasites in samples obtained from pregnant women from three sub-Saharan countries. Findings support a model of local origination of the triple-mutant SGEG *dhps* haplotypes, rather than geographical diffusion.
Taylor et al. (27)	Malawi 1997–2006	Molecular analysis of samples from delivering women over 9 years. SP resistance increased, together with the proportion of women receiving IPTp-SP, but its use was not associated with poor birth outcomes or exacerbation of placental pathology.
Smith et al. (15)	Ghana 2009	User acceptability study of ISTp compared with IPTp. Both strategies appeared equally acceptable to pregnant women for the control of MiP.
Smith Paintain et al. (57)	Ghana 2009	Provider acceptability study of ISTp at the ANC clinics level. Findings suggest preference for prevention over cure, and increased workload, may be barriers to IST implementation.

Publication	Country and study years	Study description and main conclusions
Walker et al. Unpublished (14)	2015	Modelling study on the African areas of need for more effective intervention than IPTp-SP, given the development of SP resistance and on the relative possible effectiveness of ISTp.
Williams et al. Unpublished (58)	Gambia, Mali, Burkina Faso and Ghana 2010–12	Description of non-falciparum malaria infections among pregnant women participating in the multicentre RCT comparing ISTp with IPTp-SP conducted in west Africa (*11*).
Williams et al. Unpublished (21)	Ghana 2010–12	Description of the performance of RDT used in the RCT comparing IST and IPTp conducted in Ghana (*11*). The sensitivity of the RDT used was high at enrolment but declined during the course of pregnancy. RDT negative malaria infections were uncommon during pregnancy and not associated with adverse birth outcomes, but the number of women with these infections was small.
Yore et al. Unpublished (59)	Ghana, Kenya, United Republic of Tanzania and Uganda	Preliminary results of the WHO pilot pregnancy registry project.

Annex 2 Additional information on artemisinin exposure in early pregnancy, performed after the evidence review group (ERG) meeting

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Table A2.1 Number of documented confirmed first-trimester exposures to artemisinins

Author	Country	Publication year	Number of confirmed first-trimester exposures	AL	AS[a]	MAS	AS-SP	Art (IV/IM)	AQAS	DHA-PPQ
McGready (42)	Myanmar–Thai border	Updated and not yet published	301	14	188	89		5[b]		5
Deen (60)	Gambia	2001	77				77			
Adam (61)	Sudan	2009	62	3			11	48		
Manyando (62)	Zambia	2010	156	156						
Rulisa (63)	Rwanda	2012	96	96						
Mosha (64**)**	United Republic of Tanzania	2014	168	168						
Poespoprodjo (65)	Indonesia	2014	18					10		13
Dellicour (66, 67)	Kenya	Not yet published	85	85						
Sevene (67)	Mozambique	Not yet published	21	21						
Tinto (67)	Burkina Faso	Not yet published	41	1					40	
Total			**1025**	**544**	**188**	**89**	**88**	**58**	**40**	**18**

AL, artemether-lumefantrine; AQAS, amodiaquine-artesunate; AS, artesunate; AS-SP, artesunate-sulfadoxine-pyrimethamine; Art, artesunate; DHA-PPQ, dihydroartemisinin-piperaquine; IM, intramuscular; IV, intravenous; MAS, mefloquine-artesunate.

a AS for 7 days either as monotherapy n=147; or as a non-fixed combination including AS + Clindamycin n=36; AS + Doxycycline n=3; AS + atovaquone-proguanil n=2.

b Includes one women treated with artemether IM for 6 days

Level of risk excluded for miscarriages and stillbirths

A recent meta-analysis of seven prospective cohort studies found no increase in the risk of pregnancy loss (miscarriage or stillbirth) associated with artemisinin exposures early in pregnancy. The risk of miscarriage was lower in pregnancies exposed to artemisinin in the first trimester compared to quinine, with a hazard ratio of 0.45 (95% confidence interval [CI]: 0.27–0.75). For stillbirth, the corresponding hazard ratio was 0.81 (95% CI: 0.22–2.95) and thus suggests a similar risk in pregnancies exposed to artemisinin and quinine in the first trimester, although the upper limit of the 95% CI cannot rule out increases in risk that are <2.95-fold (Table A2.2). Smaller numbers were available for exposures occurring during the putative embryo-sensitive period for artemisinin compounds (4–10 inclusive weeks post conception corresponding to 6–12 weeks post last menstrual period, LMP). The upper limit of the 95% CI of the hazard ratio rules out a 1.55-fold or greater increase in risk of miscarriage and a 4.63-fold or greater increase in risk of stillbirth.

Table A2.2 Hazard ratio and 95% CI for the risk of miscarriage and stillbirth associated with artemisinin exposures compared to quinine exposures in early pregnancy

	Artemisinin compound # events/ # total	Quinine # events/ # total	Adjusted HR (95% CI)	*P*-value
Miscarriage				
First trimester (2–14 weeks post LMP)	27/ 604	85/ 595	0.45 (0.27–0.75)	0.002
Embryo-sensitive period (6–12 weeks post LMP)	22/ 406	49/ 333	0.93 (0.55–1.55)	0.773
Stillbirth				
First trimester (2–14 weeks post LMP)	11/ 560	5/ 107	0.81 (0.22–2.95)	0.745
Embryo-sensitive period (6–12 weeks post LMP)	9/ 383	3/ 57	1.69 (0.62–4.63)	0.309

CI, confidence interval; HR, hazard ratio; LMP, last menstrual period
Hazard ratios account for pregnancy-week under observation through left-truncation and treat exposure as time-dependent variable. Estimates were derived through random effect aggregate data meta-analysis.

Level of risk detectable for major malformations

For all artemisinin compounds combined, sufficient numbers of first-trimester exposures (n=1025) have been monitored to detect at least a 2.1-fold increase in risk of overall major congenital malformations (see Table A2.3 for assumptions). No such increases have been detected to date. For AL, sufficient numbers of first-trimester exposures (n=544) have been monitored to detect at least a 2.6-fold increase in risk of overall major congenital malformations. There are insufficient data to make similar comparisons for other specific artemisinin combinations or compounds or specific subgroups of defects.

For exposures occurring during the putative embryo-sensitive period for artemisinin compounds, it is estimated that 615 out of 1025 documented first-trimester exposures occurred between 6–12 weeks post LMP (about 60% of the first-trimester exposures based on the prospective studies included in the meta-analysis). This number is sufficient to detect at least a 2.5-fold increase in risk of overall major congenital malformation. For AL, sufficient numbers of exposures (n=326) in the putative embryo-sensitive period have been monitored to detect at least a 3.1-fold increase in risk of overall major congenital malformations.

Table A2.3 Minimum level of increase in relative risks for congenital malformations that can be ruled out, according to the number of confirmed exposed pregnancies for each artemisinin treatment type (power 80% and one-sided α=0.05). The exposed to unexposed ratios are based on the number observed from published studies and unpublished studies included in the meta-analysis: for first trimester the ratio is 1:25 and for embryo-sensitive period it is 1:44. These sample size calculations are based on a one-sided approach because pregnancy exposure registries are designed to detect safety signals rather than to examine potential protective effects. Based on the formula for cohort design described in Strom's Pharmacoepidemiology (68): N=1/[p(1-R)]2x [Z 1-α√((1+1/k)U(1-U))+Z1-β√(pR(1-Rp)+(P(1-P))/k)]2 where p is the incidence of disease in unexposed; R is the minimum relative risk to detect; k is the ratio of unexposed controls to exposed; and U=(Kp+pR)/(k+1).

	Any artemisinin compound	AL	ASa	MAS	AS-SP	Art (IV/IM)	AQAS	DHA-PPQ
First-trimester exposures	1025	544	188	89	88	63	40	18
Major malformations (*P*=0.7%)[b]	2.1	2.6	4.0	5.9	5.9	7.1	9.5	15.5
Specific birth defect (*P*=0.1%)	4.6	6.4	12.5	21.5	22.0	28.0	41.0	80.0
Exposures in embryo-sensitive period[c]	615	326	112	53	52	37	24	10
Major malformations (*P*=0.7%)	2.5	3.1	5.1	7.6	7.7	9.5	12.5	25.0
Specific birth defect (*P*=0.1%)	5.9	8.4	17.2	30.0	31.0	41.0	56.0	120.0

AL, artemether-lumefantrine; AQAS, amodiaquine-artesunate; AS, artesunate; AS-SP, artesunate-sulfadoxine-pyrimethamine; Art, artesunate; DHA-PPQ, dihydroartemisinin-piperaquine; IM, intramuscular; IV, intravenous; MAS, mefloquine-artesunate

[a] Treatment categories are not mutually exclusive as some cases were exposed to multiple class of artemisinin treatment.

[b] Based on major malformations detectable at birth by systematic surface examination observed across studies to date.

[c] Estimated at 60% of all first-trimester exposures based on studies included in the meta-analysis.

Annex 3 List of ERG meeting participants

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GLOBAL MALARIA PROGRAMME

World Health Organization

WHO Evidence Review Group on Intermittent Screening and Treatment (ISTp) and ACT Treatment of Malaria in Pregnancy

Malaria Policy Advisory Committee
Geneva, Switzerland
16-18 September 2015

Rose Gana Fomban Leke
Larry Slutsker
Co-Chairpersons, WHO ERG on MiP
July 2015

Outline

- Background
- Objectives
- Process
- Key Conclusions
- Recommendations

Background

- In October 2012, on the advice of the Malaria Policy Advisory Committee (MPAC) after the work of a dedicated evidence review group (ERG), WHO updated the policy for IPTp with sulphadoxine-pyrimethamine (IPTp-SP). The new policy recommends that women living in areas of moderate to high malaria transmission should receive IPTp-SP as early as possible in the second trimester, and at each scheduled antenatal care (ANC) visit thereafter, with SP doses given at least one month apart.
- In 2013, the MPAC concluded that there was insufficient data to determine at what level of SP resistance IPTp-SP should be discontinued in the absence of an established and effective alternative and to define the level of Plasmodium falciparum transmission at which IPTp-SP may cease to be cost-effective from a public health point of view.

Background

- ALTERNATIVES: several studies have been completed on the efficacy, safety, feasibility, acceptability and cost-effectiveness of alternative interventions to prevent the consequences of malaria in pregnancy, including intermittent screening and treatment of malaria in pregnancy (ISTp).
- During recent years, a growing body of evidence has been accumulated on the clinical safety of the artemisinin derivatives in the first trimester of pregnancy, and of the efficacy of different artemisinin-based combination therapies (ACTs) in treatment of uncomplicated malaria in pregnancy.
- To review these studies and in order to update WHO recommendations, WHO/GMP convened an ERG with specific focus on the efficacy of ISTp compared with IPTp and the safety of artemisinin derivatives in early pregnancy.

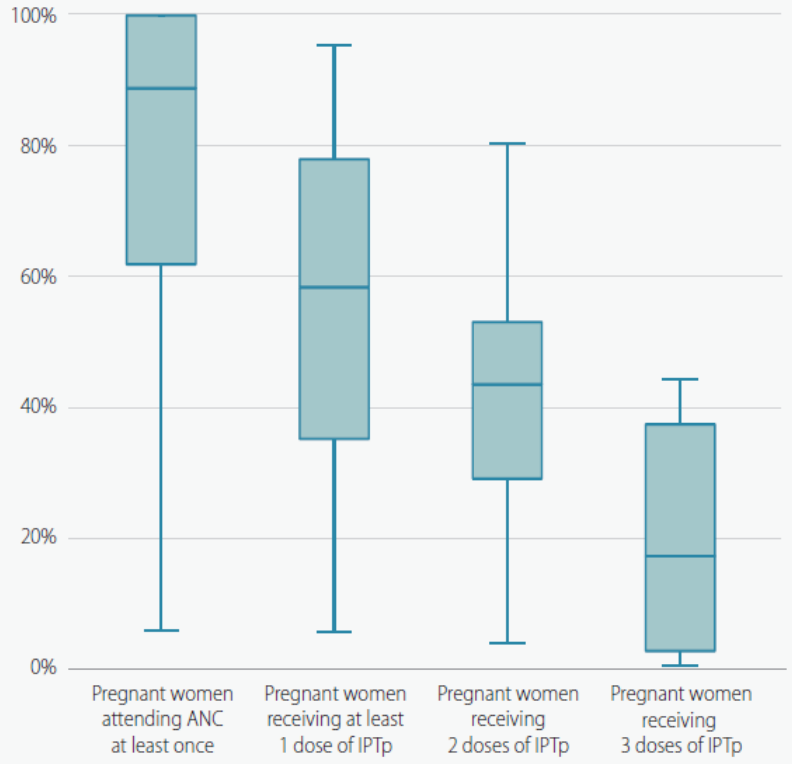
Objectives of the ERG meeting

Part 1. To review the available evidence on the efficacy, safety, acceptability and cost-effectiveness of intermittent screening and treatment of malaria in pregnancy (ISTp) using rapid diagnostic tests and different antimalarial medicines as a potential alternative strategy for intermittent preventive treatment of malaria in pregnancy (IPTp)

Part 2. To review the efficacy and safety data on the use of artemisinin-based combination for the treatment of uncomplicated malaria during pregnancy, with specific attention to exposure in the first trimester as compared to quinine, in view of possible revisions of current recommendations for malaria treatment in the first trimester of pregnancy.

Missed opportunities for delivering IPTp in 2013: stagnant increase of IPTp uptake since 2007

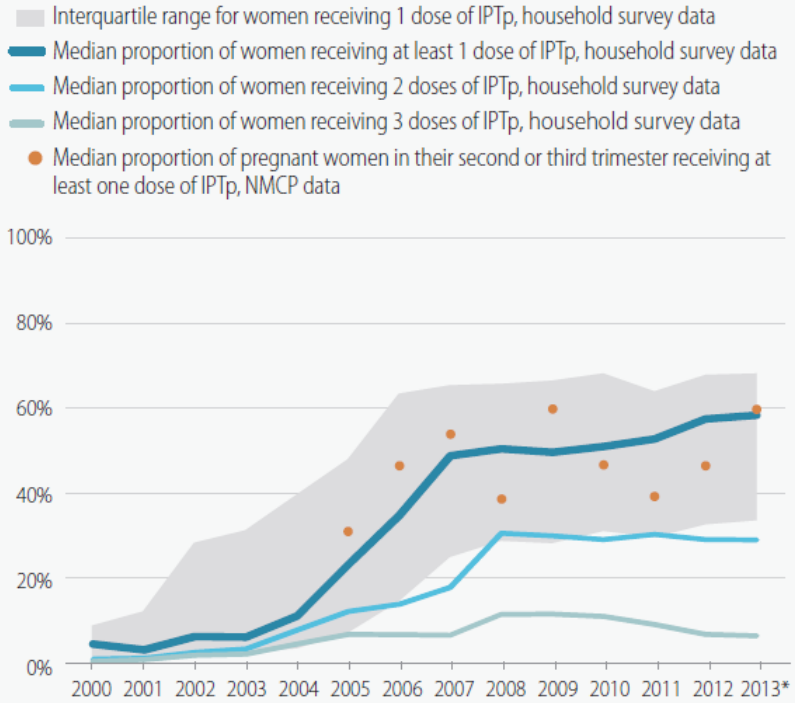
Figure 4.1 Proportion of pregnant women attending ANC and proportion receiving IPTp, by dose, among sub-Saharan countries reporting, 2013



ANC, antenatal care; IPTp, intermittent preventive treatment in pregnancy

Source: *National malaria control programme reports, UN population estimates*

Figure 4.2 Proportion of pregnant women receiving IPTp, by dose, by year of pregnancy in survey and by reporting year for NMCP, Africa, 2000–2013

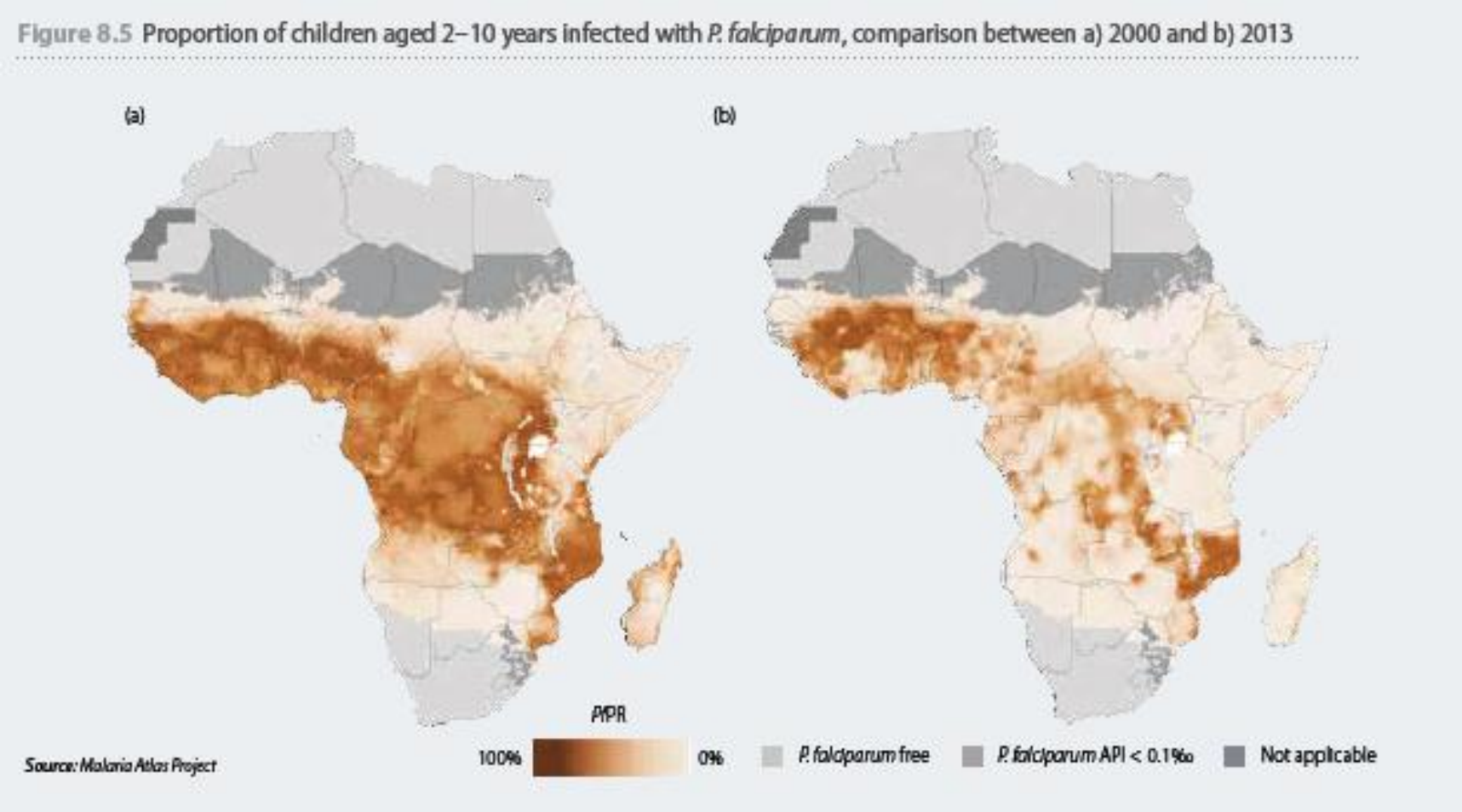


IPTp, intermittent preventive treatment in pregnancy; NMCP, national malaria control programme

* Median proportions using household data are based on six-year trend analyses

Source: *Demographic health surveys, malaria indicator surveys, multiple indicator cluster surveys and other household survey data, NMCP reports, UN population estimates*

Proportion of children aged 2-10 years infected with *P. falciparum*: a) 2000 and b) 2013



ERG areas of review in relation to potential alternatives to IPTp-SP (Part I)

1. Review all available published and unpublished reports on the efficacy, and safety of ISTp compared to IPTp for prevention of the adverse consequences of malaria in pregnancy.
2. Review available reports on the acceptability of ISTp under trial conditions.
3. Review results of cost-effectiveness analyses (CEA) of ISTp.
4. Review the recent evidence on the effect of submicroscopic infections on maternal and infant outcomes.
5. Review available published and unpublished reports on the impact of SP resistance on IPTp-SP effectiveness.
6. Review results of recently completed clinical trials evaluating the efficacy and safety of DHA-PPQ for IPTp.
7. Based on the evidence reviewed, consider if either ISTp or IPTp with DHA-PPQ could be recommended as a potential alternative to IPTp-SP in some areas with high SP resistance and/or very low transmission.

Current WHO recommendations for treatment of uncomplicated malaria in the 1st trimester of pregnancy

Guidelines for the treatment of malaria • 3RD EDITION

Treating uncomplicated *P. falciparum* malaria in special risk groups

First trimester of pregnancy

Treat pregnant women with uncomplicated *P. falciparum* malaria during the first trimester with 7 days of quinine + clindamycin.

Strong recommendation, very low- quality evidence

- …in the absence of adequate safety data on the artemisinin-derivatives in the first trimester of pregnancy the Guideline Development Group was unable to make recommendations beyond reiterating the status quo.

ERG areas of review in relation to ACT safety in early pregnancy (Part II)

8. Review the evidence of embryotoxicity of artemisinin derivatives from animal studies.
9. Review available published and unpublished reports on exposures to artemisinin derivatives in the first trimester of pregnancy.
10. Review results of recent clinical trials evaluating the efficacy and safety of different ACTs for malaria treatment in the second and third trimester of gestation.
11. Based on the evidence reviewed, consider if the current WHO recommendations on use of ACTs in pregnancy could be updated.

Participants and dynamics of the ERG meeting

ERG meeting Part 1 – ISTp	ERG meeting part I2 – ACT Rx
Chairpersons: Rose G. F. Leke & Larry Slutsker Rapporteur: Raquel Gonzalez	
Presenters: M. Cairns, P. Deloron, M. Desai, S. Fernandes, K. Hanson, J. Hill, H. Hopkins, A. Kakuru, M. Madanitsa, C. Roper, H. Tagbor, S. Taylor, P. Walker, J. Webster	Presenters: R. Clark, U. d'Alessandro, S. Dellicour, U. Metha, E. Pelfrene, E. Sevene, A. Stergachis, T. Wells
Presenters: B. Greenwood, J. Gutman, R. Mc Gready, C. Menendez, F. Ter Kuile	
Reviewers: P. Don Mathanga, P. Kremsner (part II), M. Laufer, L. Mbuagbaw, B. Nahlen, H. Noedl (II), M. Nyunt, N. Padilla, S. Rogerson, E. Roman	
Observer: D. Kyabayinze	Observer: S. Duparc
WHO Secretariat: P. Alonso, A. Barette, A. Bosman, G.M. Mbemba, J. Namboze, P. Olumese, S. Schwarte	

Process

- . All participants contributed to the sessions in plenary and in working groups, but only the independent reviewers and WHO Secretariat attended a final closed session to elaborate the recommendations of the meeting.

DOCUMENT: REPORT

- The key conclusions emerging from the topics are presented as summarised "**Key conclusions**", inboxes, at the end of the respective sections of the report.
- The main conclusions and recommendations of the meeting, reviewed and agreed among the independent reviewers are presented as the last section of the report and summarised at beginning of the document.

Pre-reads, Presentations and Discussions

- ISTp compared to IPTp with SP in West and East Africa
- Acceptability of ISTp under trial conditions
- Cost-effectiveness of ISTp
- Effects of submicroscopic infections on maternal and infant outcomes
- Impact of SP resistance and malaria transmission on IPTp-SP effectiveness
- Evaluation of DHA-PPQ for IPTp
- Embryotoxicity of artemisinin derivatives in animal studies
- Safety of artemisinin exposure in the first trimester of pregnancy
- Efficacy and safety of ACTs in the 2nd and 3rd trimester of pregnancy
- General considerations on antimalarials use in pregnancy

ISTp Compared to IPTp with SP in West and East Africa

Key conclusions

- ISTp (either with SP or AL as treatment) was not inferior to IPTp with SP in preventing third trimester maternal anemia, LBW and placental malaria in studies conducted in areas of low SP resistance in West Africa.
- However, the incidence of outpatient visits and malaria episodes during pregnancy was higher in ISTp group compared to IPTp-SP.
- The results from the trials conducted in West Africa suggest that **IPTp with SP should be continued where SP resistance is low.**
- ISTp with DHA-PPQ was not superior to IPTp-SP in areas of high malaria transmission and high SP resistance of East and Southern Africa and was associated with more malaria during pregnancy and at delivery in all gravidae and lower mean birth weight in paucigravidae.
- **IPTp with SP retains some of its effectiveness in areas of high SP resistance and should be continued in these areas.**

Acceptability of ISTp under trial conditions

Key conclusions

- Overall, **ISTp** (either with AS-AQ or DHA-PPQ) was considered to be an **acceptable alternative to IPTp with SP both by providers and users in trial conditions**.
- Quality of care of ANC services as well adherence to a three-day course of treatment were concerns perceived by pregnant women and health care workers respectively.
- Further research would be needed to confirm these findings in larger studies, other settings and in non-trial conditions.

Cost-effectiveness of ISTp

Key conclusions

- **ISTp** (with AL) was found to be **more expensive and less effective** for prevention of MiP than IPTp with SP.
- **At the current levels of efficacy of IPTp with SP, it would not be cost-effective to switch from IPTp-SP to ISTp-AL.**

Effects of submicroscopic infections on maternal and infant outcomes

Key conclusions

- **Submiscroscopic infections,** especially early in pregnancy were associated **with maternal anaemia, LBW and prematurity.**
- The effects of submicroscopic infections on adverse pregnancy outcomes need to be confirmed in large longitudinal studies and in different settings.
- **Malaria infection prevalence is highest at the antenatal booking visit** and declines thereafter. **The sensitivity of RDTs is also highest at the initial visit, in particular in primigravidae.** Thus, the use of RDTs to screen asymptomatic pregnant women for malaria infection is likely to be most beneficial at the first antenatal visit.

Impact of SP resistance and malaria transmission on IPTp-SP effectiveness

Key conclusions

- **IPTp with SP remains effective** in preventing the adverse consequences of malaria on maternal and infant outcomes, including in areas where quintuple mutant haplotypes *Plasmodium falciparum* mutations to SP are highly prevalent.
- The **association between *dhfr* 581G mutation and decreased low birth weight** in women receiving IPTp with SP compared to non-recipient of SP reported in limited areas from Tanzania has not been observed in other sub-Saharan countries and its potential impact on IPTp-SP effectiveness **requires further investigation**.
- **Further research on the impact of other SP resistance markers on IPTp-effectiveness should be done** in sub-Saharan countries where IPTp-SP is used.
- There is currently **no evidence of a threshold level of malaria transmission below which IPTp-SP is no longer cost-effective.**

Evaluation of DHA-PPQ for IPTp

Key conclusions

- Recent studies evaluating **DHA-PPQ for IPTp** have found that the drug was **more efficacious than SP in reducing maternal malaria infection and anemia at** delivery, **incidence of malaria** during pregnancy, **stillbirths** and infant mortality within 6-8 weeks.

- These **promising results** would need to be confirmed in larger RCT involving women in areas with similar malaria transmission and SP resistance and in areas with different malaria transmission and SP resistance levels.

- In addition, the **safety** of administering repeated doses **of DHA-PPQ** (with specific attention to QTc prolongation) requires **further investigations** as well as adherence to the required three-day regimen for each DHA-PPQ treatment dose and the safety of DHA-PPQ co-administration with antiretrovirals in HIV-infected women.

Embryotoxicity of artemisinin in animal studies

Key conclusions

- **Embryo deaths and malformations induced by artemisinin** derivatives have been reported in **rats, rabbits and monkeys**. The effects are dose and time dependent.
- By extrapolation of animal toxicity findings it is possible to estimate in humans a putative sensitive embryonic period between start of week four to the end of week ten post-conception, or from the start of week six to the end of week 12 post LMP.

Safety of artemisinin in the first trimester of pregnancy

Key conclusions

- Updated evidence on the safety of artemisinin indicates that **ACT exposure in first trimester of pregnancy does not increase the risk of miscarriage, stillbirths or major congenital malformations compared to quinine.**
- Women treated with an artemisinin anytime during first trimester were at similar or lower risk of miscarriage compared to those treated with oral quinine.
- Based on the available updated evidence, the first line treatment of uncomplicated malaria in the first trimester of pregnancy should be revised to include ACTs as therapeutic option.
- Most of the data of artemisinin exposure in the first trimester of pregnancy are from AL exposure and consequently, more safety data are needed with other ACTs
- There is a need for **continued monitoring and pharmacovigilance of drug exposure in early pregnancy, including more information on congenital malformations.**

Post-ERG meeting updated analyses

Additional information on artemisinin exposure in early pregnancy, performed after the ERG meeting

S. Dellicour and E. Sevene, R. McGready, H. Tinto, D. Mosha, C. Manyando, S.Rulisa, M. Desai, P. Ouma, E.Macete, C.Menéndez, G. Calip, O. Augusto, K. A. Moore, F. Nosten, F.ter Kuile, A. Stergachis

Table 1. Number of documented confirmed 1st trimester exposures to artemisinins.

Author	Country	Publication Year	Number of confirmed first trimester exposures	AL	AS*	MAS	AS-SP	Art (IV/IM)	AQAS	DHA-PPQ
McGready[41]	Thai-Myanmar Border	Updated and not yet published	301	14	188	89		5^		5
Deen[60]	Gambia	2001	77				77			
Adam[61]	Sudan	2009	62	3			11	48		
Manyando[62]	Zambia	2010	156	156						
Rulisa[63]	Rwanda	2012	96	96						
Mosha[64]	Tanzania	2014	168	168						
Poespoprodjo[65]	Indonesia	2014	18					10		13
Dellicour[66,67]	Kenya	Not yet published	85	85						
Sevene[67]	Mozambique	Not yet published	21	21						
Tinto[67]	Burkina Faso	Not yet published	41	1					40	
Total			**1025**	**544**	**188**	**89**	**88**	**58**	**40**	**18**

*AS for 7 days either as monotherapy n=147; or as a non-fixed combination including AS+Clindamycin n=36; AS + Doxycycline n=3; AS + atovaquone-proguanil n=2;
^ Includes one women treated with Artemether IM for 6 days.

Acronyms: AL, artemether-lumefantrine; AQAS, amodiaquine-artesunate; AS, artesunate; AS-SP, artesunate-sulphadoxine-pyrimethamine; Art, artesunate; DHA-PPQ, dihydroartemisinin-piperaquine; IM, intramuscular; IV, intravenous; MAS: mefloquine-artesunate.

Post-ERG meeting updated analyses

Risk of miscarriage and stillbirth with artemisinin and quinine exposures in early pregnancy.

	Artemisinin compound # events/ # total	Quinine # events/ # total	Adjusted HR (95%CI)	P-value
Miscarriage				
1st trimester (2-14 weeks post-LMP)	27/ 604	85/ 595	0.45 (0.27- 0.75)	0.002
Embryo-sensitive period (6-12 weeks post-LMP)	22/ 406	49/ 333	0.93 (0.55- 1.55)	0.773
Stillbirth				
1st trimester (2-14 weeks post-LMP)	11/ 560	5/ 107	0.81 (0.22, 2.95)	0.745
Embryo-sensitive period (6-12 weeks post-LMP)	9/ 383	3/ 57	1.69 (0.62, 4.63)	0.309

The upper limit of the 95% CI of the hazard ratio rule out a 1.55-fold or greater increase in risk of miscarriage and a 4.63-fold or greater increase in risk of stillbirth.

Post-ERG meeting updated analyses

Risk detectable for major malformations

	Any artemisinin compound*	AL	AS*	MAS	AS-SP	Art (IV/IM)	AQAS	DHA-PPQ
1st trimester exposures	1025	544	188	89	88	63	40	18
Major Malformations (p=0.7%)**	2.1	2.6	4.0	5.9	5.9	7.1	9.5	15.5
Specific Birth Defect (p=0.1%)	4.6	6.4	12.5	21.5	22.0	28.0	41.0	80.0
Exposures in embryo-sensitive period ***	615	326	112	53	52	37	24	10
Major Malformations (p=0.7%)	2.5	3.1	5.1	7.6	7.7	9.5	12.5	25.0
Specific Birth Defect (p=0.1%)	5.9	8.4	17.2	30.0	31.0	41.0	56.0	120.0

* Treatment categories are not mutually exclusive as some cases were exposed to multiple class of artemisinin treatment

** Based on major malformations detectable at birth by systematic surface examination observed across studies to date.

*** Estimated at 60% of all 1st trimester exposures based on studies included in the meta-analysis.

Acronyms: AL, artemether-lumefantrine; AQAS, amodiaquine-artesunate; AS, artesunate; AS-SP, artesunate-sulphadoxine-pyrimethamine; Art, artesunate; DHA-PPQ, dihydroartemisinin-piperaquine; IM, intramuscular; IV, intravenous; MAS: mefloquine-artesunate.

Minimum level of increase in relative risks for congenital malformations that can be ruled out, according to the number of confirmed exposed pregnancies for each artemisinin treatment type (Power 80% and one-sided α=0.05).

Efficacy and safety of ACTs in the 2nd and 3rd trimester of pregnancy

Key conclusions

- Data on **ACTs use for treatment of clinical uncomplicated malaria** in second and third trimesters of pregnancy indicate that they are **safe in terms of pregnancy outcomes and efficacious** to clear *Plasmodium* parasites (especially DHA-PPQ).
- ACTs can be thus considered a safe and efficacious option for treatment of clinical uncomplicated malaria in women in the second and third trimester of gestation.

General considerations on antimalarials use in pregnancy

Key conclusions

- More **studies in HIV-infected pregnant women** are needed, including evaluation of **mother to child transmission and drug interactions** between antimalarials and antiretrovirals.

WHO experience

In 2012, WHO recommended the use of efavirenz as first line treatment of HIV infection in pregnancy despite pre-clinical data showing embryotoxicity, based on comprehensive reviews of safety data in pregnant women and programmatic superiority to standard of care. A similar approach could be followed to support an updated WHO recommendation of ACT use in first trimester of pregnancy.

Draft recommendations (I)

- IPTp with SP remains highly cost-effective in preventing the adverse consequences of malaria on maternal and fetal outcomes, and should thus be aggressively scaled-up in line with the current WHO recommendations. IPTp with SP also remains effective in areas where quintuple mutant haplotypes of Plasmodium falciparum to SP are highly prevalent.
- The association between sextuple mutant haplotypes of *P. falciparum* and decreased low birth weight (LBW) reported in limited areas in Tanzania with very high SP resistance in the context of observational studies using retrospective information about the assignment of SP, has not been observed in other sub-Saharan countries in the context of randomised controlled trials with SP, and requires further investigation. In these limited geographic areas with very high SP resistance, the benefits and cost-effectiveness of adding at the first ANC visit a single RDT screening and treatment to the continued provision of IPTp with SP, should be evaluated in pilot studies.

Draft recommendations (II)

- There is currently no evidence of a threshold level of malaria transmission below which IPTp-SP is no longer cost-effective. Therefore, in areas where IPTp with SP is implemented and transmission reduced to low levels as a result of successful control strategies, WHO recommends continued implementation until the area has been targeted for malaria elimination by the national programme.
- Recent studies have shown that intermittent screening and treatment (IST) with RDTs and ACTs of pregnant women at ANC resulted in a higher proportion of maternal infections and clinical malaria during pregnancy and lower mean birth weight compared with IPTp-SP. Further, being less cost-effective than IPTp with SP, ISTp with the currently available RDTs should not be recommended as an alternative to IPT-SP.

Draft recommendations (II)

- Recent studies have shown that IPTp with dihydroartemisinin-piperaquine (DHA-PPQ) did not reduce low birth weight compared to IPTp with SP, but was more efficacious in reducing maternal malaria parasitemia and anemia at delivery, incidence of malaria infection and clinical malaria during pregnancy, stillbirths and early infant mortality within 6-8 weeks. More research is needed to evaluate the impact of DHA-PPQ for IPTp on LBW, safety of repeated doses and adherence to the required three-day regimen.

Draft recommendations (III)

- New evidence from 1025 pregnancies with confirmed artemisinin exposure in first trimester indicate that artemisinins do not increase the risk of miscarriage, stillbirths or major congenital malformations compared to women with malaria treated with non-artemisnin regimens. Moreover, comparison of carefully documented and prospectively collected safety data on women exposed to only artemisinin-based treatment with those collected on women exposed to only quinine in the first trimester of pregnancy showed that artemisinin was associated with a significantly reduced rate of miscarriage compared to quinine. Therefore, the WHO recommendations for the treatment of clinical uncomplicated malaria episodes in women in the first trimester of pregnancy should be updated as follows: "Treat pregnant women with uncomplicated P. falciparum malaria with either the first line ACT for three days or quinine and clindamycin for seven days". Artemether-lumefantrine (AL) should be the preferred ACT, as most of the available data derive from AL exposure.

Draft recommendations (III)

- Although the evidence regarding the safety of ACTs in early pregnancy has been strengthened by the recent review, there is the need for continued monitoring of drug safety, birth outcomes and neonatal mortality. Moreover, potential drug-drug interactions in HIV-infected pregnant women who are taking antiretrovirals and receive antimalarials as well as the risk of mother to child transmission should also be monitored.

Global **Malaria** Programme

Intermittent screening and treatment in pregnancy and the safety of ACTs in the first trimester

NOVEMBER 2015

RECOMMENDATIONS

BACKGROUND

Malaria in pregnancy is a major, preventable cause of maternal morbidity and poor birth outcomes. To prevent these adverse outcomes, WHO recommends the use of insecticide treated mosquito nets and effective case management of malaria and anaemia in pregnant women. In areas of moderate to high malaria transmission of sub-Saharan Africa, WHO also recommends intermittent preventive treatment in pregnancy (IPTp) with sulphadoxine-pyrimethamine (SP). In recent years an alternative strategy, consisting of intermittent screening and treatment in pregnancy (ISTp) using rapid diagnostic tests (RDTs) and treatment with artemisinin-based combination therapies (ACTs) during antenatal care (ANC) visits, has been evaluated in several countries. Moreover, multiple studies have assessed the safety of using ACTs in the first trimester of pregnancy.

RECOMMENDATIONS

Based on a recent WHO evidence review(*1*), the following recommendations are made on the use of IPTp and ISTp in pregnancy and on the safety of ACTs in the first trimester.

1. Recent comparative studies have shown that intermittent screening and treatment in pregnancy (ISTp) with RDTs and ACTs resulted in a higher proportion of maternal infections and clinical malaria during pregnancy compared to intermittent preventive treatment in pregnancy (IPTp) with SP given during ANC visits. The effects of ISTp on birth weight varied. In some studies, ISTp with artemether-lumefantrine was not inferior to IPTp in preventing low birth weight. In other studies, ISTp with dihydroartemisinin-piperaquine (DHA-PPQ) resulted in a lower mean birth weight compared with

World Health Organization

IPTp-SP in paucigravidae in areas of high malaria transmission and high SP resistance. ISTp is also less cost-effective than IPTp-SP and, for these reasons, it is not recommended as an alternative to IPTp-SP.

2. IPTp-SP remains highly cost-effective in preventing the adverse consequences of malaria on maternal and fetal outcomes, and should therefore be actively scaled up in line with the current WHO recommendations. IPTp-SP also remains effective in areas where quintuple-mutant haplotypes of Plasmodium falciparum to SP are highly prevalent. Further research on the relationship of SP resistance markers and IPTp effectiveness should be done, particularly in areas where transmission and thus maternal immunity have declined substantially in recent years.

3. The threshold level of malaria transmission below which IPTp-SP is no longer cost-effective has not been identified. Therefore, in areas where IPTp-SP is implemented and transmission has been reduced to low levels as a result of successful control strategies, WHO recommends continued IPTp-SP implementation until the area approaches interruption of transmission.

4. An association between sextuple mutant haplotypes of P. falciparum and decreased birth weight has been reported in observational studies in a few sites in East Africa. Further studies are required to assess this and to devise the best and most cost-effective prevention strategies in areas of very high SP resistance. One potential strategy to be tested is to provide a single RDT screening and ACT treatment at the first ANC visit during the second trimester, in addition to the continued delivery of IPTp-SP.

5. Recent studies have shown that IPTp with dihydroartemisinin-piperaquine (DHA-PPQ) does not reduce the incidence of low birth weight compared to IPTp-SP, but that it is more efficacious in reducing maternal malaria parasitaemia and anaemia at delivery, incidence of malaria infection and clinical malaria during pregnancy, and stillbirths and early infant mortality (i.e. within 6–8 weeks). More research is needed to evaluate the impact of DHA-PPQ for IPTp in preventing low birth weight, safety of repeated doses, and adherence to the required 3-day regimen.

6. New evidence from 1025 pregnancies with confirmed artemisinin exposure in the first trimester in South-East Asia and sub-Saharan Africa indicates that artemisinins are not associated with an increased risk of miscarriage, stillbirths or major congenital malformations compared to non-artemisinin regimens. Moreover, comparison of carefully documented and prospectively collected safety data on women exposed only to artemisinin-based treatment with data collected on women exposed only to quinine in the first trimester of pregnancy showed that artemisinin was associated with a significantly reduced rate of miscarriage compared to quinine. MPAC recommends the review of the WHO Guidelines for the treatment of malaria to consider the timely inclusion of ACTs as a first-line therapeutic option for uncomplicated falciparum malaria.

REFERENCES

1. The report available on the WHO Global Malaria Programme website at http://www.who.int/malaria/mpac/mpac-sept2015-erg-mip-report.pdf

WHO/HTM/GMP/2015.9

GLOBAL MALARIA PROGRAMME

World Health Organization

Update on Policy Setting Process for WHO/GMP

Malaria Policy Advisory Committee
Geneva, Switzerland
16-18 September 2015

Pedro Alonso
Director, Global Malaria Programme

Principles for organizing TEGs/ERGs

1. **TEGs are positioned as WHO committees steered by GMP Units to serve the goals & mandates of WHO**

2. **TEGs are product-driven and associated with clear deliverables**
   - Core positioning as working groups rather than 'sounding boards' for the Units
   - Can provide advice on department's activities & strategic questions

3. **All guidelines integrated into the "Malaria prevention & treatment guidelines handbook" and reviewed by the WHO Guidelines Review Committee (GRC)**
   - WHO GRC not used for SM&E deliverables

4. **Existing TEGs reformulated and establish two new TEGs to reflect GMP priorities**
   a. Drug resistance, SM&E and Vector Control TEGs membership rotation to reflect membership
   b. Add diagnostic experts to Chemotherapy TEG, as needed
   c. Create new TEGs on Financing, Coverage & Impact and Elimination (not immediately)

5. **MPAC consulted on key strategic issues where its input is needed**

6. **ERGs used as ad hoc bodies to provide draft recommendations to MPAC on specific technical topics**
   - Not a sub-group of TEGs, but separate entities

1. If needed, consider creating a separate Diagnostics TEG in second phase

Membership & ways of working

Membership in each TEG limited (exact number to be defined - 12)

Full TEG meetings limited to one per year – exceptionally two if circumstances demand it

Diversity of members ensured (geographies, genders & expertise)

Programmatic experience required on all TEGs

TEGs to have one Chair (and potentially one Deputy Chair) – rather than two co-Chairs

Participation of MPAC members to TEGs not mandatory, and a maximum of two MPAC members by TEG or ERG accepted

- MPAC member participation should always be justified

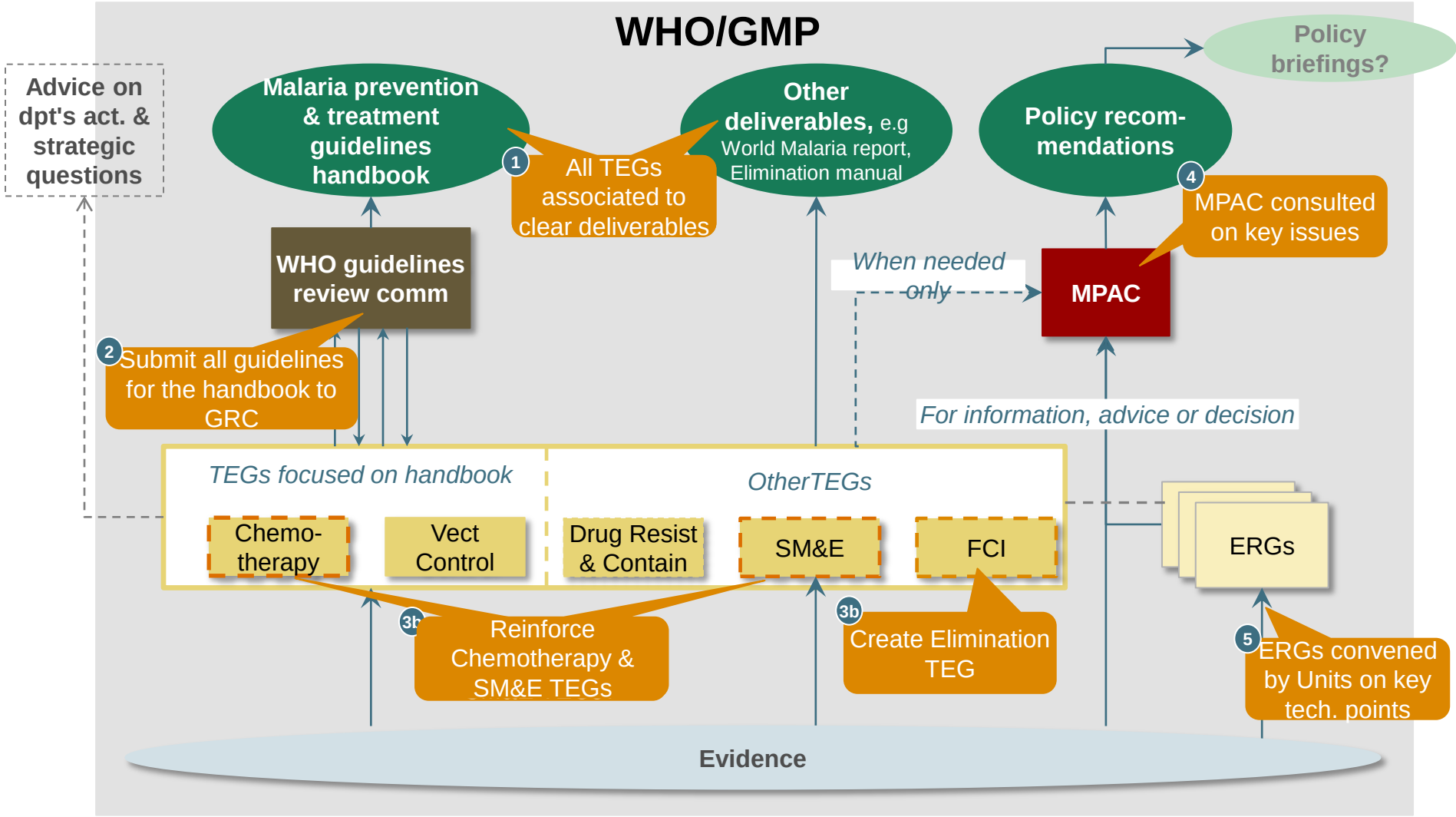
Standard observer rules applied to all TEGs / ERGs

- Invited observers accepted in open sessions of all TEGs/ERGs
- No standing observers accepted
- But possibility of holding "closed sessions" when necessary

New members to benefit from standard induction process

- Including information on expected behaviour, e.g. that they not talk to the press of their work in the TEGs/ERGs

Policy-Setting Process at WHO/GMP



Technical Expert Groups

- **Chemotherapy TEG:** is tasked with reviewing evidence, providing guidance and making draft recommendations on issues of malaria diagnosis and use of antimalarial medicines both for treatment and prevention.

- **Antimalarial Drug Efficacy & Response TEG:** is tasked with reviewing evidence, providing guidance and making draft recommendations on issues of drug efficacy, resistance and response. While the issue of resistance to artemisinins is of urgent concern, resistance to other antimalarial medicines is also of prime importance.

- **Vector Control TEG:** is tasked with reviewing and developing guidance on the implementation of malaria vector control including issues related to programme management.

- **Surveillance, Monitoring & Evaluation TEG:** is tasked with reviewing evidence, summarizing progress, providing guidance and making draft recommendations on issues related to surveillance, monitoring and evaluation.

- **Financing, Coverage & Impact TEG:** is tasked with reviewing the current status of malaria control, identifying critical issues regarding the financing and implementation of the GTS 2016-2030, and making draft recommendations on issues related to (i) programme financing, (ii) achieving universal coverage of malaria interventions (iii) maximizing programme impact.