Malaria Policy Advisory Committee Meeting

11–13 April 2018, Geneva, Switzerland
Background document for Session 6

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

September 2018
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Background

Owing to recent progress in malaria control, including the use of specific forms of preventive chemotherapy (e.g. seasonal malaria chemoprevention), the drive towards malaria elimination and the availability of new antimalarial medicines, there has been renewed interest in the role mass drug administration (MDA) can play in several settings.

Currently, WHO recommends MDA to interrupt falciparum malaria transmission in areas approaching elimination; to reduce the risk of spread of multi-drug resistance in the Greater Mekong subregion; during malaria epidemics; and in exceptional complex emergencies [1]. Based on field experience acquired over the past 10 years, WHO has recently released a practical manual on MDA for malaria to support operations [2].

WHO's current recommendations on the use of MDA for malaria elimination are based on a very limited number of studies. The Cochrane Systematic Review on MDA for malaria [3] is currently being updated to include new studies that have been conducted in areas of low to very low transmission since 2013. This review is expected to be completed by July 2018.

Since the last WHO evidence review on MDA in April 2015 [3], several large-scale trials have been implemented to evaluate the role of MDA combined with other core interventions in accelerating progress towards malaria elimination in areas of moderate transmission.[1] In particular, MDA with artemisinin+piperaquine has been implemented in the Comoros Islands in combination with LLINs, with DHA+piperaquine in the Magude Province of Mozambique together with IRS (pirimiphos-methyl), and with DHA+piperaquine in the Southern Province of Zambia in combination with LLINs. In Mozambique and Zambia, these interventions have been implemented over two years and results from these trials will soon be available in publications for review.

Following the successful implementation of MDA with artesunate+amodiaquine (ASAQ) completed in 2015 in Sierra Leone at the peak of the Ebola epidemic, WHO supported an MDA programme to complement vector control and case management in children under 5 in Nigeria's Borno State – an area of declared public health emergency – in order to rapidly reduce malaria mortality in this population. Four rounds of MDA with ASAQ were

[1] Moderate transmission areas have an annual parasite incidence of 250–450 cases per 1000 population and a prevalence of *P. falciparum/P. vivax* malaria of 10–35% (see: A framework for malaria elimination. Geneva: World Health Organization; 2017 (http://apps.who.int/iris/bitstream/10665/254761/1/9789241511988-eng.pdf).

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implemented from July to November 2017, integrated into polio campaigns. These interventions reached a total of 1.2 million children, and early results suggest a reduction of malaria cases in Borno State [5]. Similar interventions of age-targeted MDA for malaria, integrated into vaccination and food distribution campaigns, are also being introduced in South Sudan in order to reduce malaria mortality in children exposed to intense malaria transmission and complex emergencies.

Objectives of the WHO Evidence Review Group

1. To determine the effectiveness of MDA combined with other core interventions in reducing malaria incidence and prevalence in areas of moderate transmission, with particular attention to the effects of vector control, case management and intensified surveillance on the effectiveness of MDA, and the length of time over which reduction in malaria transmission is sustained post-MDA.
2. To review new evidence on the impact of MDA in areas of low to very low transmission in relation to current WHO recommendations on MDA for interrupting falciparum malaria transmission in areas approaching elimination and reducing the risk of spread of multi-drug resistance in the Greater Mekong subregion.
3. To review evidence and experience with age-targeted MDA as an intervention to reduce malaria mortality in children exposed to intense malaria transmission and complex emergencies.

Process

Three GMP units, Prevention Diagnostics and Treatment together with Elimination and Technical Support and Capacity Building, will collaborate on the technical preparations for the meeting. The PDT unit will provide administrative support, with support from the Bill & Melinda Gates Foundation umbrella grant.

WHO/GMP will convene a group of 12 independent experts in elimination and complex emergencies from national malaria programmes and leading technical agencies, as well as methodology experts in the assessment of data from applied field research.

Representatives of national malaria programmes and collaborating technical and research institutions (e.g. CDC Atlanta, CISM, Guangzhou University of Traditional Medicine, ISGlobal, LSTM, PATH and STPH) will be invited to present results from MDA trials in areas of moderate transmission and complex emergencies, as well as systematic reviews on MDA in areas of low to very low transmission.

The ERG meeting will involve up to 25 participants and will require 2 days, with 24–25 September proposed as tentative dates.

A compilation of the recent studies on MDA for malaria, kindly shared by the Malaria Eradication Scientific Alliance (MESA), is presented in the Annex below.

References

1. The role of mass drug administration, mass screening and treatment, and focal screening and treatment for malaria. Geneva: World Health Organization; 2015 (http://www.who.int/malaria/publications/atoz/role-of-mda-for-malaria.pdf).
2. Mass drug administration for falciparum malaria: a practical field manual. Geneva: World Health Organization; 2017 (http://apps.who.int/iris/bitstream/10665/259367/1/9789241513104-eng.pdf).
3. Poirot E, Skarbinski J, Sinclair D, Kachur SP, Slutsker L, Hwang J. Mass drug administration for malaria. Cochrane Database Syst Rev. 2013;12:CD008846. doi:10.1002/14651858.CD008846.pub2.
4. Mass drug administration, mass screening and treatment and focal screening and treatment for malaria: WHO Evidence Review Group meeting report. Geneva: World Health Organization; 2015 (http://www.who.int/entity/malaria/mpac/mpac-sept2015-erg-mda-report.pdf).
5. World malaria report 2017. Geneva: World Health Organization; 2017 (http://apps.who.int/iris/bitstream/10665/259492/1/9789241565523-eng.pdf).

Title of study	Objectives	Countries (Pf/Pv)	Timeline	Methodology	Primary outcomes measured	Size of the target population (people, households, villages)	Leading institution	Funding source	Additional information
Assess the micro-epidemiology of resistant falciparum malaria in SE Asia, and perform and evaluate an intervention with targeted chemo-elimination through a modified mass drug administration approach	Assess the safety and acceptability of TME to eliminate the sub-microscopic reservoir of Pf in an area of ART resistance Assess the feasibility of MDA with DHP+P Assess the impact of MDA with DHP+P on the sub-microscopic reservoir Study the re-emergence of Pf if and when it occurs Explore the extent to which the sub-microscopic reservoir contributes to transmission	Cambodia (Pf/Pv)	2014 – Oct 2016	• Cluster randomized • Mass drug administration • 3 rounds of treatment with 28 day intervals • Dihydro-artemisinin-piperaquine (DHP) + primaquine (P)	Parasite prevalence measured by qPCR	2 villages control & 2 villages intervention	MORU (Nick White & Arjen Dondorp)	Gates Foundation; Wellcome Trust	https://clinicaltrials.gov/ct2/show/NCT01872702
Assess the micro-epidemiology of resistant falciparum malaria in SE Asia, and perform and evaluate an intervention with targeted chemo-elimination through a modified mass drug administration approach	Assess the safety and acceptability of TME to eliminate the sub-microscopic reservoir of Pf in an area of ART resistance Assess the feasibility of MDA with DHP+P Assess the impact of MDA with DHP+P on the sub-microscopic reservoir Study the re-emergence of Pf if and when it occurs Explore the extent to which the sub-microscopic reservoir contributes to transmission	Myanmar/Thailand (Pf/Pv)	2015 – Oct 2016	• Cluster randomized • Mass drug administration • 3 rounds of treatment with 28 day intervals • Dihydro-artemisinin-piperaquine (DHP) + primaquine (P)	Parasite prevalence measured by qPCR	2 villages control & 2 villages intervention	MORU (Nick White & Arjen Dondorp)	Gates Foundation	http://www.malariaeradication.org/mesa-track/assess-micro-epidemiology-resistant-falciparum-malaria-se-asia-and-perform-and-evaluate-1

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Assess the micro-epidemiology of resistant falciparum malaria in SE Asia, and perform and evaluate an intervention with targeted chemo-elimination through a modified mass drug administration approach	Assess the safety and acceptability of TME to eliminate the sub-microscopic reservoir of Pf in an area of ART resistance Assess the feasibility of MDA with DHP+P Assess the impact of MDA with DHP+P on the sub-microscopic reservoir Study the re-emergence of Pf if and when it occurs Explore the extent to which the sub-microscopic reservoir contributes to transmission	Laos (Pf/Pv)	2015 – Oct 2016	• Cluster randomized • Mass drug administration • 3 rounds of treatment with 28 day intervals • Dihydro-artemisinin-piperaquine (DHP) + primaquine (P)	Parasite prevalence measured by qPCR	2 villages control & 2 villages intervention	MORU (Nick White & Arjen Dondorp)	Gates Foundation	

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Assessing the effectiveness of household-level focal mass drug administration and community-wide mass drug administration with dihydroartemisinin + piperaquine for reducing malaria parasite infection prevalence and incidence in Southern Province Zambia	To assess the effectiveness of FDA and MDA with DHA-Pip against no mass treatment for reducing P. falciparum parasite prevalence	Zambia (Pf)	2014 – Sept 2015	• Cluster randomized controlled trial with three arms: • Arm 1: 2 rounds of Mass Test with Mass Drug Administration • Arm 2: 2 rounds of Mass Test with Focal Drug Administration • Arm 3: Control • RDTs • DHA-Pip : 2 rounds of treat-ment 1 month apart	Parasitaemia prevalence in children 1 month to <6 years old;Incidence of passively detected Pf cases;Incidence of infection in longitudinal cohort	4 districts – Population 417 000	Macepa (John Miller &Thomas Eisele)	Gates Foundation	http://goo.gl/46r0UA
Community reactive case detection versus reactive drug administration in malaria elimination areas: a cluster randomized controlled trial	To compare the effectiveness of case investigation with reactive focal drug administration using dihydroartemisinin + piperaquine versus case investigation with reactive focal testing and treatment using artemether-lumefantrine in reducing malaria prevalence and incidence within highly supervised research health posts	Zambia (Pf)	2014 – Sept 2015	• Cluster randomized controlled trial with two arms: • Arm 1: Case investigation with reactive focal test and treat using artemether-lumefantrine: • Arm 2: Case investigation with reactive focal drug administration using DHA-Pip	Incidence of passively detected Pf cases; Malaria parasite prevalence as measured by PCR	Population 80 000	Akros (Dan Bridges)	Gates Foundation	http://goo.gl/H1SztC

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Defining effective, appropriate, implementable strategies for malaria elimination in military forces in Cambodia as a model for mobile migrant populations within the Greater Mekong Subregion (GMS)	To evaluate approaches to malaria elimination with the Royal Cambodian Armed Forces. It will compare a screening and treatment approach vs. use of malaria prophylaxis. Intervention will be used in conjunction with low-dose primaquine and an insecticide-treated uniform. Cost-effectiveness of various diagnostic approaches will be compared.	Cambodia (Pf/Pv)	Mar 2014 – Dec 2015	• Four research groups compared: tMDA and MSAT, each with and without an intensive vector control approach. • MSAT: DHP + primaquine if/when blood stage positive • tMDA: Monthly DHP + primaquine x 3 months			AFRIMS (David Saunders)	Gates Foundation	http://goo.gl/j3SSh6
Developing the evidence for and assessing the feasibility of malaria elimination efforts among mobile migrant workers in plantation settings in Cambodia and Myanmar	Test different active 'screen and treat' models in selected plantations to identify the most cost-effective, sustainable and operationally feasible test and treat approaches for plantation workers	Myanmar/ Cambodia (Pf/Pv)		• Approach 1: Screen and treat on arrival and on exit from the plantation • Approach 2: Screen and treat all workers at fixed intervals, such as every 3 months • Approach 3: If epidemiological data demonstrate that the majority of workers harbour malaria parasites, MDA in one site may be done. • Dihydro-artemisinin + piperaquine			PSI (Ricki Oxford)	Gates Foundation	http://goo.gl/A84RBG

Title of study	Objectives	Countries (Pf/Pv)	Timeline	Methodology	Primary outcomes measured	Size of the target population (people, households, villages)	Leading institution	Funding source	Additional information
Eliminating Plasmodium falciparum with ACTs in sub-Saharan Africa	To support improved surveillance and determine the suitability of Targeted Parasite Elimination (TPE) using ACT as a new strategy for malaria elimination	Namibia (Pf)	Jan 2014 – Dec 2017				UCSF (Roly Gosling)	Novartis & Global Environment Fund	http://goo.gl/qXaDlO

Title of study	Objectives	Countries (Pf/Pv)	Timeline	Methodology	Primary outcomes measured	Size of the target population (people, households, villages)	Leading institution	Funding source	Additional information
Evaluating the feasibility and effectiveness of Reactive Targeted Parasite Elimination vs. Reactive Case Detection as a community-level intervention in response to a passively identified index case: a cluster randomized controlled trial in Swaziland	Primary aim: To compare the impact of TPE versus RACD on malaria incidenceSecondary aimsEffectiveness: 1. To compare the impact of TPE versus RACD on seroprevalence2. To compare the impact of TPE versus RACD on prevalence of infection3. To compare the impact of TPE versus RACD on proportion of imported to local incident cases, and time to first post-intervention incident local case4. To compare the impact of TPE versus RACD on transmission potential as measured by relatedness of infections by microsatellite genotypingFeasibility:1. To determine the feasibility of reaching 80% coverage for TPE and compare coverage to RACD2. To evaluate the safety of TPE3. To compare the acceptability of TPE versus RACD4. To compare the costs and cost-effectiveness of TPE versus RACD 5. To measure adherence to a modified DOT regimen	Swaziland (Pf)	Jan 2014 – Dec 2016	• Cluster randomized controlled trial • Targeted Parasite Elimination (TPE) vs. reactive case detection • DHA-Pip			UCSF (Roly Gosling)	Gates Foundation	http://goo.gl/MruUQj

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Evaluation of targeted mass drug administration and reactive case detection on malaria transmission and elimination in Ethiopia	Will the addition of tMDA or reactive case detection conducted within a 100m radius of the index case in a setting of optimized malaria control interventions impact community-level malaria transmission?	Ethiopia (Pf/Pv)					Addis Continental Institute of Public Health (AC-IPH), Ethiopia	President's Malaria Initiative (PMI)	http://www.malariaeradication.org/mesa-track/evaluation-targeted-mass-drug-administration-and-reactive-case-detection-malaria
Four-arm trial of reactive Targeted Parasite Elimination (TPE): use of presumptive treatment vs. reactive case detection +/- vector control in Namibia in response to incident malaria	Primary aim: To compare the impact of TPE versus RACD on malaria incidence	Namibia (Pf)	End date: Dec 2017	• Arm 1: RACD as per programme – RDT screening and treatment • Arm 2: RACD + IRS with Actellic CS to EA after first reported cases • Arm 3: Focal MDA (household and immediate neighbours) in response to a case • Arm 4: Focal MDA + IRS with Actellic CS • DHP - Once daily x 3 days for each incident case • AL - Standard age-specific treatment dosing			UCSF (Michelle S. Hsiang)	Gates Foundation	

Title of study	Objectives	Countries (Pf/Pv)	Timeline	Methodology	Primary outcomes measured	Size of the target population (people, households, villages)	Leading institution	Funding source	Additional information
Impact of two annual cycles of mass drug administration on temporal trends of clinical malaria	To observe impact on human reservoir of infection and transmission	Gambia (Pf)	2013 – 2015	• 1 round MDA annually for 2-year period • Dihydro-artemisinin-piperaquine (DHP)	Malaria incidence and prevalence, adverse events	6 village pairs across 5 regions of Gambia	MRC Unit The Gambia (Julia Mwesigwa presented at ASTMH)	MRC UK	ASTMH video http://www.malariaeradication.org/knowledge-hub/astmh-2017-julia-mwesigwa-%E2%80%9Cimpact-two-annual-cycles-mass-drug-administration-temporal
Mass drug administration of DHA-PQP to accelerate towards malaria elimination in Magude district, Southern Mozambique	To implement a mass drug administration campaign to target asymptomatic malaria infections in a district of Mozambique with the final goal of interrupting transmission. DHA-PQP will be administered in two rounds, one month apart.	Mozambique (Pf)	2015 – June 2017	• 2 rounds of mass drug administration, 1 month apart • Dihydro-artemisinin-piperaquine (DHP) + primaquine (P)	Parasite prevalence detected by RDT and/or PCR		Maltem - CISM/ISGlobal (Francisco Saute)	Gates Foundation	http://goo.gl/htlh4p
New surveillance tool for malaria elimination in Myanmar	1. Identify reservoirs of sub-patent asymptomatic P. falciparum parasitaemia in Myanmar using ultra-sensitive qPCR on finger-stick samples, providing "real-time intelligence" to guide elimination; 2. Implement TME pilot evaluations at sites within Myanmar to be selected based upon results of surveillance data	Myanmar (Pf/Pv)		• Daily dihydro-artemisinin-piperaquine for 3 days in months 1, 2 and 3; single-dose primaquine on day 1 of each month			University of Maryland (Chris Plowe)	Gates Foundation	http://goo.gl/eNoYVe

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Speeding up malaria elimination; a cluster randomized controlled trial of mass drug administration in Southeast Myanmar, an area with artemisinin resistance	Primary endpoint qPCR Pf at 5, 10, 15, 21 months from start of MDASecondary endpoints: Proportion of Kelch 13 mutations in Pf infections, number of MDA participants with adverse events, incidence of symptomatic Pf infections in the study area, prevalence of non-Pf infections in the study area	Myanmar (Pf/Pv)	June 2014 – Jan 2017	• Paired cluster randomized controlled trial • MDA plus routine malaria interventions vs routine malaria interventions alone • MDA: DHP (dihydroartemisinin-piperaquine) for 3 days and single-dose primaquine for 3 consecutive months • Routine: LLIN distribution and village health workers using RDTs, AL (artemether-lumefantrine) for Pf infections and chloroquine for Pv infections • Venous blood for PCR analysis	Primary endpoint qPCR P.falciparum at 5, 10, 15, 21 months from start of MDA	Target population between 75 and 1200 people per village. 58 villages close to Thai border screened for eligibility, 8 village pairs randomized	Myanmar Oxford Clinical Research Unit (James Heaton ASTMH presenter)	Global Fund Regional Artemisinin-resistance Initiative (RAI)	ASTMH 2017 video http://www.malariaeradication.org/knowledge-hub/astmh-2017-james-heaton-%E2%80%9Cspeeding-malaria-elimination-cluster-randomized-controlled
Targeted malaria elimination in Karen state, Myanmar	To decrease the prevalence of clinical and sub-clinical P. falciparum infections in a defined area where artemisinin resistance has been documented (control activities) and then to proceed with elimination of the parasite reservoirs (elimination activities)	Myanmar (Pf/Pv)					MORU (Lisa White)	Gates Foundation	

Title of study	Objectives	Countries (Pf/Pv)	Timeline	Methodology	Primary outcomes measured	Size of the target population (people, households, villages)	Leading institution	Funding source	Additional information
The Haiti Malaria Elimination Consortium (HaMEC)	Assess the performance of the targeted malaria elimination (TME) strategy as measured against set targets so that the TME strategy can be improved and adapted to address any operational issues that are identified; Document where indigenous malaria transmission has been successfully interrupted, as well as where it has not, in an effort to focus TME strategies accordingly;Identify programme and external factors that lead to the success and failure of achieving malaria elimination;Track the overall progress towards malaria elimination in Haiti as a precursor to elimination certification	Haiti (Pf)	Feb 2015 – March 2017				CDC & Tulane	Gates Foundation	http://goo.gl/I4jSQ7

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Using MDA to rapidly reduce malaria transmission in Ebola-affected areas of Sierra Leone	1. Rapidly reduce malaria-related incidence and mortality rates by providing intervalled MDA using ASAQ – targeting seven high-burden districts and all populations (all ages including children under 5 and pregnant women);2. Rapidly reduce number of febrile Ebola suspected episodes that would otherwise have required screening and isolation in the Ebola suspected holding centres to exclude Ebola as the cause of illnesses; and reduce the risk of Ebola transmission among malaria patients	Sierra Leone (Pf)					WHO & NMCP Sierra Leone (Maru Aregawi/ Samuel Smith)		http://www.malariaeradication.org/mesa-track/using-mda-rapidly-reduce-malaria-transmission-ebola-affected-areas-sierra-leone