Global **Malaria** Programme

WHO Malaria Policy Advisory Committee (MPAC) meeting

OCTOBER 2017

MEETING REPORT

SUMMARY

On 17–19 October 2017, the WHO Malaria Policy Advisory Committee (MPAC) convened to review updates and progress, and provide guidance with respect to specific thematic areas of work carried out by the Global Malaria Programme (GMP).

The meeting included 10 sessions focused on 18 topics: (1) the outcomes from an evidence review group (ERG) on low density infections; (2) the outcomes from an ERG on the deployment of piperonyl butoxide plus pyrethroids nets; (3) an update on malaria elimination in the Greater Mekong Subregion; (4) the outcomes from the drug efficacy and response technical expert group (TEG); (5) a response plan on *pfhrp2* gene deletions; (6) an update on RTS,S pilot implementation; (7) an update on the malaria vaccine advisory committee; (8) an update on the vector control advisory group; (9) the outcomes of the ERG on comparative effectiveness of vector control tools; (10) a proposed ERG on border malaria; (11) an introduction to the WHO Research & Development Observatory; (12) a presentation on universal access to malaria core interventions ; (13) the results from the rapid access expansion programme on integrated community case management of malaria; (14) a demonstration of the online mapping tool for insecticide resistance, antimalarial resistance and *hrp2/3* deletion data; (15) the outcomes of the ERG on malaria in pregnancy outside of Africa; (16) an update on the establishment of the malaria elimination oversight committee (MEOC) and malaria elimination certification panel (MECP); (17) a proposed ERG on malaria mortality estimates; and (18) a review of the revised recommendations for achieving and maintaining universal coverage with long-lasting insecticidal nets in malaria control.

At the closing session, the key outcomes/recommendations of MPAC to GMP included:

- **Low density infections:** MPAC agreed with the standardization of the terminology suggested by the ERG, reviewed the suggestions for updating the WHO recommendations on the diagnosis of *P. falciparum*

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and *P. vivax* malaria in low transmission settings and endorsed the proposed updates with some modifications.

- **Deployment of PBO plus pyrethroids nets:** MPAC endorsed the recommendations of the ERG with the note that specifying "metabolic pyrethroid resistance" should be updated throughout the document. MPAC also noted that the largest benefit of the pyrethroid-PBO nets was in areas of moderate metabolic pyrethroid resistance, but that available data indicate that this class of nets performs at least as well as or better than pyrethroid-only LLINs across all settings where any level of pyrethroid resistance due to a metabolic resistance mechanism is present. The online version of the recommendations will be updated accordingly.

- **Elimination in the Greater Mekong Subregion:** MPAC welcomed reported progress in the GMS as evidenced by declines in national incidence across the subregion. MPAC requested that future reports be based on a more detailed analysis that includes subnational data on incidence reductions and progress in those areas in the GMS with documented transmission of multidrug resistant (MDR) *P. falciparum*.

- **Drug efficacy & response:** MPAC supported the initiative to develop updated guidance for prevention and treatment of MDR *P. falciparum* as an extension of the current *Global plan for artemisinin resistance and containment* (GPARC). MPAC also supported continued research into treatment options for MDR including triple therapy and/or sequential approaches. MPAC urged GMP to work with donors and partners to ensure that an adequate stockpile of artemisinin combination therapies (ACTs) are available for programme use.

- **Response plan on *pfhrp2* gene deletions:** MPAC noted the progress that has been made since the last update and supported the global response plan with suggestions for the outcome-based actions, coordination and prioritization.

- **RTS,S pilot implementation:** MPAC noted the progress made to date and was in favour of the development of the proposed framework for policy decision making.

- **Malaria vaccine advisory committee (MALVAC):** MPAC supports the reconvening of MALVAC with the suggestion that the purpose of the committee must be made clear.

- **Vector control advisory group (VCAG):** MPAC requested that VCAG, and WHO more generally, explore ways to further simplify its processes and definitions in the assessment of the public health value of new vector control tools. A review of current documentation should specifically clarify the algorithms for how decisions are made, with the goal of increasing understanding of the process among development partners. A specific area requiring further clarity is how insecticide-treated nets are being evaluated when compared to other vector control interventions, given that the current definition of "class" and "entomological effect" do not support current classification of different new generation nets. MPAC also recommended that the WHO guidance for insecticide resistance management be updated including the use of non-pyrethroid/multiple active ingredient long-lasting insecticidal nets as insecticide resistance management tools analogous to the rotation of insecticides for indoor residual spraying covered in the *Global plan for insecticide resistance management* (GPIRM). Finally, MPAC noted that the cost implications of evidence-generation are beyond the scope of VCAG and highlighted the need to work with partners to identify incentives including accelerated funding for key evidence generating trials.

- **Comparative effectiveness of vector control tools:** MPAC agreed that SumiShield® 50WG meets the current WHO efficacy criteria for indoor residual spraying and has a similar entomological effect to other products that are currently covered by a WHO policy recommendation. Based on this assessment, MPAC recommended that the existing WHO policy for IRS be extended to include SumiShield® 50WG. Specific ERG recommendations on the evaluation of other new tools were accepted as presented in the draft recommendations shared with MPAC.

- **Border malaria:** MPAC supported the convening of the ERG on border malaria and noted that border issues are long-standing and are often a political issue as much as a technical issue for malaria control and elimination programmes. MPAC urged the Secretariat to reach out to national malaria control programmes to help frame the questions to be considered by the ERG and to include an analysis of successes and challenges already learned.

- **Global Observatory on Health R&D:** MPAC appreciated the opportunity to contribute to the thinking on how to prioritize investments in malaria R&D and suggested that if malaria is being used as a pathfinder, perhaps WHO should look at the cross-disease relevance of investments.

- **Universal access to malaria core interventions:** MPAC noted that overall, countries are not on target to meet the GTS milestones for 2020 on burden reduction and agree that action is needed urgently to reduce malaria morbidity and mortality by targeting coverage of core interventions of vector control, diagnosis and treatment, chemoprevention and surveillance.

- **Rapid access expansion programme results:** MPAC noted the positive results of the RAcE programme and highlighted that there is a wealth of historical evidence that demonstrates the impact of introducing well-trained, supervised and supplied community health workers (CHWs). MPAC further noted that the challenge to maintaining the impact of CHWs is to include them as health system personnel delivering a countrywide intervention.

- **Malaria Threats Map:** MPAC noted the progress of the Malaria Threats Map tool and felt that it is a useful platform for making global threats data available.

- **Malaria in pregnancy outside of Africa:** MPAC noted the conclusions of the ERG and agreed that no new recommendations are needed based on the data reviewed.

- **Malaria elimination oversight committee and malaria elimination certification panel:** MPAC agreed that it was important to separate the functions of the groups and clarified the expected role of MPAC in reviewing the panel reports and endorsing recommendations for malaria-free certification to the Director-General.

- **Malaria mortality estimates:** MPAC supported the convening of an ERG for malaria mortality estimates and noted three key issues to consider: 1) the need to develop methods to estimate the burden of indirect deaths from malaria; 2) the need to ensure the engagement of country programmes especially those with highest burden and weak surveillance systems, so as for them to understand the estimation approaches and provide input; and 3) expansion of the ERG to include the methods for estimating malaria morbidity as these require further discussion and have implications for mortality estimation.

- **Achieving universal coverage with long-lasting insecticidal nets:** MPAC endorsed the revised recommendations with some minor adjustments to the text.

BACKGROUND

The WHO Global Malaria Programme (GMP) convened the Malaria Policy Advisory Committee (MPAC) for its twelfth meeting in Geneva, Switzerland on 17–19 October 2017. MPAC convenes twice annually in Geneva to provide independent strategic advice to WHO on policy recommendations for malaria control and elimination. The Committee is supported by technical expert groups (TEGs) and ad hoc evidence review groups (ERG), whose work focuses on thematic areas and specific research questions to generate sufficient evidence to provide guidance. Over the course of the three-day meeting's open sessions, 14 MPAC members, six national malaria control programme managers, the WHO Secretariat and 40 observers discussed the updates and progress in the work areas presented. Recommendations were discussed in the final closed session of the committee.

UPDATES FROM THE GLOBAL MALARIA PROGRAMME

The GMP Director opened the meeting by providing a concise general update on the work of the WHO-GMP units organized according to the five roles articulated in the Strategy: 1) Address key malaria control and elimination strategic questions; 2) set, communicate & disseminate evidence-based normative guidance, policy advice and implementation guidance to support country action; 3) coordinate WHO capacity building & technical support to Member States, jointly with regions and countries; 4) help countries develop and implement robust surveillance systems to generate quality data and use those data to achieve greater impact; 5) keep an independent score of global progress in malaria control and elimination, including drug & insecticide resistance. Key strategic concerns include an analysis of malaria mortality and coverage gaps, prioritizing the R&D pipeline for malaria, and a reassessment of the current contribution of malaria to the burden of anaemia. The Director highlighted new normative guidance that has been launched since the last meeting, the work to strengthen policy dissemination, technical support to Member States and capacity building activities that have been undertaken, work on surveillance to improve routine data and analysis, and updates on the *World Malaria Report* and the Malaria Threats Map. Visits to the GMP website have increased steadily since 2014 and communications around World Malaria Day and other high level events have increased web traffic. The Director closed with a reminder of the 2020 GTS milestones and the number of countries that are not on track.

SUMMARY OF THE MPAC SESSIONS

Outcomes from evidence review group on low density malaria infections

Background: In March 2014, WHO published recommendations on the use of malaria diagnostics in low transmission settings.[1] The application of nucleic acid amplification (NAA) based diagnostic tools in epidemiological investigations and targeted elimination efforts has expanded, and highly sensitive, non-NAA-based point-of-care-methods have been developed and commercialized. Therefore, WHO convened an ERG to review the previous recommendations based on new evidence and the natural history, prevalence, contribution to transmission, and public health importance of detecting and treating low-density *P. falciparum* and *P. vivax* infections. The ERG determined that the

terminology moving forward should be low density infections, rather than asymptomatic or submicroscopic infections.

MPAC conclusions: MPAC agreed with the standardization of the terminology and reviewed the suggestions for updating the previous WHO recommendation on the diagnosis of *P. falciparum* and *P. vivax* malaria in low transmission settings. MPAC endorsed the update with some modifications:

- A number of highly sensitive techniques are available that detect low-density infections (below 100 parasites/µl). There is currently insufficient evidence to assess whether detection of low-density infections using these tools will have a significant impact on transmission. Until such evidence is generated these tools should be further evaluated through research activities and are not recommended for deployment in routine malaria control or elimination programmes.

- Quality-assured conventional RDT and microscopy are the recommended diagnostic tools for the confirmation and management of malaria cases and malaria surveillance, including routine health information systems and household surveys, in all epidemiological settings. Malaria cases should be reported by type of diagnostic test used.

- The majority of infections with asexual parasites (including those infections with low-density parasitaemia) have gametocytes and therefore all malaria infections must be considered as potentially infectious. There is no demonstrated benefit of routine detection of low-density gametocytemia by molecular methods.

- Presentation of NAA results should include details of the methods used for sample collection and extraction, and the quantity of blood added for the PCR reaction, as well as details of outputs in DNA copies or parasite density.

- The role of serological assays in malaria elimination programmes is not known. In addition, reagents (antigens and controls), assay methodologies and analytical approaches used in these assays need to be standardized and validated.

Other issues that were raised during the discussion were the possible use of highly sensitive malaria tests in research; to collect information on the cost-effectiveness of detecting and treating low density infections; to develop a methodology framework for research on low density infections in all epidemiological settings, including elimination as well as in moderate to high transmission settings; to explore the importance of detecting low density infections in passive and active case detection strategies; to evaluate the impact of reactive case detection or focal or mass test and treatment approaches with these tests; and to investigate whether these tests are of value in managing malaria in pregnancy.

Outcomes from evidence review group on deployment of piperonyl butoxide plus pyrethroids nets

Background: An ERG was convened to consider new data on the potential public health value of a pyrethroid net containing the synergist piperonyl butoxide (PBO). On the basis of the available evidence, the ERG concluded that one epidemiological study in an area with resistance has demonstrated that pyrethroid-PBO nets have additional public health value over standard LLINs, and recommended that pyrethroid-PBO nets receive an interim endorsement as a new WHO class of vector-control products. The ERG

further recommended that national malaria control programmes and their partners consider deployment of pyrethroid-PBO nets in areas where pyrethroid resistance has been confirmed in the main malaria vectors, but only if universal coverage with effective vector control can be maintained. The ERG also called for the generation of further evidence on pyrethroid-PBO nets to support refinement of WHO guidance regarding the conditions for the deployment of this class of product:

MPAC conclusions: MPAC endorsed recommendations of the ERG with the note that specifying "metabolic pyrethroid resistance" should be updated throughout the document. MPAC noted that the largest benefit of the pyrethroids-PBO nets is likely to occur in areas of moderate pyrethroid resistance, but that available data indicate that this class of nets performs at least as well as or better than pyrethroid-only LLINs across other settings where pyrethroid resistance due to a metabolic resistance mechanism is present. It was requested that this should be clarified in the recommendations available online.

Update on malaria elimination in the Greater Mekong Subregion (GMS)

Background: An update was provided on the trends, strategy, Malaria Mekong Elimination Team and support, therapeutic efficacy study sites, pharmacology support, regional coordination, country progress and challenges in the subregion.

MPAC conclusions: MPAC welcomed reported progress in the GMS as evidenced by declines in national incidence across the subregion. MPAC noted that it is critically important to keep on target for reduction/ elimination goals, particularly given the ongoing challenge of multidrug resistant (MDR) *P. falciparum* in the subregion. MPAC requested that future reports be based on a more detailed analysis that includes data on incidence reductions and progress in those areas in the GMS with documented transmission of MDR *P. falciparum*. MPAC noted the importance of and need for country specific operational plans detailing specific elimination activities. MPAC further noted progress achieved in data sharing and harmonization of partner activities and the key role of WHO in this effort. The ongoing challenge of the continued availability of oral artemisinin monotherapy as documented by recent market survey data was noted with concern, and MPAC urged the rapid formulation of a specific response plan. MPAC noted that future progress will be dependent on a strong commitment to elimination from national programmes. Any challenges or barriers to such commitment will need to be explored and addressed proactively.

Outcomes from the Drug Efficacy & Response Technical Expert Group

Background: GMP convened the technical expert group on Drug Efficacy and Response which developed draft recommendations on three sessions: 1) molecular markers – genotyping and monitoring drug resistance; 2) monitoring the prophylactic effect of preventive treatment; and 3) prevention and treatment of multidrug resistant malaria.

- **Piperaquine resistance -** There is sufficient evidence to confirm *Pfplasmepsin 2-3* increased copy number as a marker of piperaquine resistance in Asia. *Pfplasmepsin 2-3* increased copy number should be incorporated into surveillance and monitoring activities globally where piperaquine is being used or considered for use. *Pfkelch 13* prevalence and a growing prevalence

of *Pfplasmepsin 2-3* increased copy number should be considered in situations where a therapeutic efficacy study might not be feasible.

- **Markers of reinfection and recrudescence for *P. falciparum* -** Regarding the current guidance on *P. falciparum* genotyping in clinical trials, the use of capillary electrophoresis for *msp1*, *msp2*, and *glurp* assessment should be promoted; both molecular markers *msp1* and *msp2* should be genotyped for all samples; and PCR of different allelic families of *msp1* and *msp2* should be performed in different tubes to avoid template competition. The TEG recommends that the guidance on *P. falciparum* genotyping should be reviewed when new analyses have been completed.

- ***P. vivax* molecular markers -** There are no markers that can be used to differentiate between recrudescence, relapse, and reinfection, which makes it difficult to interpret primaquine efficacy and blood stage resistance studies. There are no molecular markers of *P. vivax* resistance to chloroquine, mefloquine, or primaquine. CYP2D6 genotyping should be included in primaquine clinical trials.

- **Monitoring the efficacy of seasonal malaria chemoprevention (SMC) –** The TEG updated its previous recommendations and noted that only limited data are available on the effect of SMC on molecular markers of resistance.

- **Strategy for antimalarial drug resistance management -** The TEG agreed that it would be valuable to have a new strategy for antimalarial drug resistance management, and that it should be developed based on the *Global plan for artemisinin resistance and containment* (GPARC) and made available as soon as possible.

- **Update on antimalarial drug efficacy and drug resistance -** The TEG recommends that all putative *Pfkelch13* mutants conferring artemisinin resistance be independently verified as being associated with resistance both in genetic studies and in the ring stage survival assay (RSA), ideally before publication claiming such an association.

- **Triple therapies –** Although data are preliminary, the data support the testing of triple therapies as a potential strategy against multidrug-resistant *P. falciparum*. Given the concern over QTc interval prolongation interval and the issues regarding the measurement of changes in QTc as malaria symptoms resolve, further analysis of QTc using alternative methods was requested by the ERG. An alternative treatment option for multidrug-resistant *P. falciparum* is to use two sequential artemisinin-based combination therapies. This approach should be tested in clinical trials.

- **Atovaquone-proguanil (AP) -** In the GMS, there may be a role for AP in combination with an ACT; artesunate-mefloquine+AP and artesunate-pyronaridine+AP are two options for testing.

MPAC conclusions: MPAC noted the evidence and progress on identifying plasmepsin 2-3 increased copy number as a useful marker for piperaquine resistance in the GMS; its relevance in sub-Saharan Africa remains to be determined. In the GMS, piperaquine resistance threatens the utility of dihydroartemisinin-piperaquine (DHA-PPQ) as a first line antimalarial treatment and thus should be closely monitored to guide ACT selection. MPAC further noted that in all malarious areas, surveillance for molecular markers of resistance to artemisinin and other ACT partner drugs is essential to guide treatment options and to monitor for emergence of resistance. MPAC supported the re-evaluation of the molecular methods and algorithm for classifying recurrent *P. falciparum* infections as reinfection or recrudescence. For *P. vivax*, further research is needed to

develop molecular methods to distinguish relapses from reinfections as current tools are not consistently reliable for this purpose. MPAC supported ongoing efforts to monitor molecular markers of resistance for amodiaquine (AQ) and sulfadoxine-pyrimethamine (SP) in the context of SMC, and looks forward to additional information as it becomes available.

MPAC supported the initiative to develop updated guidance for prevention and treatment of multidrug resistant (MDR) *P. falciparum* as an extension of the current GPARC, and looks forward to reviewing the initial draft. MPAC also supported continued research into options to address treatment for MDR including triple therapy and/or sequential approaches which may raise an issue with compliance. MPAC noted the continued monitoring and geographic extension in the GMS of the *P. falciparum* strain containing the C580Y Kelch mutation associated with artemisinin resistance. To date, there is no evidence of spread of this strain to sub Saharan Africa. MPAC further noted that the C580Y mutation has been documented in falciparum parasites in Guyana in South America, but these do not appear to be related to the GMS strain. Careful monitoring for this mutation in Guyana and surrounding countries is needed. MPAC noted that the number of ACTs failing in the GMS countries varies by area but several ACTs including artesunate-mefloquine (ASMQ) and artesunate-pyronaridine are effective antimalarial treatment for MDR *P. falciparum*. However, access to ASMQ has been problematic due to procurement challenges with the supplier. WHO should work with donors and partners to ensure an adequate stockpile of ACTs for programme use as required. MPAC reiterated that failing ACTs should not be used for treatment or for research purposes in the context of MDR resistance, as such use exerts additional selective on resistant parasites, facilitating their spread.

Global response plan to *pfhrp2* gene deletions

Background: The global response plan for *pfhrp2/3* deletions comprises a global framework to support national malaria control programmes and their implementing partners to address the problem of *pfhrp2/3* deletions that limit the programmatic effectiveness of HRP2-based rapid diagnostic tests (RDT) and put malaria patient lives at risk. The document also summarizes current knowledge and critical gaps in knowledge to guide future research and product development. The four objectives of an implemented global action plan are to:

1. define the frequency and distribution of these diagnostically relevant mutations in circulating *P. falciparum* strains;

2. provide concrete guidance to countries on malaria diagnosis and treatment in settings where such mutations are found to be frequent;