

# WHO Malaria Policy Advisory Committee (MPAC) meeting

MARCH 2017

MEETING REPORT

## SUMMARY

On 22–24 March 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 16 topics: (1) an update on the RTS,S vaccine pilot implementation programme; (2) a report on the Evidence Review Group on the cardiotoxicity of antimalarials; (3) a review of the surveillance, monitoring and evaluation operational manual; (4) an update on the development of guidelines for malaria vector control; (5) a report on the outcomes from the Evidence Review Group on *Plasmodium knowlesi*; (6) an update on the Global Vector Control Response 2017–2030; (7) a demonstration of an online mapping tool for insecticide resistance, antimalarial resistance and *hrp2/3* deletion data; (8) an update on the second meeting of the Strategic Advisory Group on malaria eradication; (9) an update on the finalization of the *Framework for malaria elimination*; (10) a report on the Evidence Review Group on the emergence and spread of multidrug resistant *Plasmodium falciparum* lineages in the Greater Mekong subregion; (11) a situation update on *hrp2/3* gene deletions; (12) a presentation of the mass drug administration for malaria practical field manual; (13) a proposed evidence review group on submicroscopic malaria infections; (14) an review of WHO policy recommendations for malaria vector control interventions; (15) a discussion on the framework for accelerating malaria elimination by 2020; and (16) proposed plans for a global call for action to ensure universal access to malaria diagnosis and treatment.

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

- **RTS,S vaccine:** MPAC congratulated GMP and partners on securing resources that will allow the Malaria Vaccine Implementation Programme to proceed. At this point, MPAC did not think it appropriate to articulate

explicit criteria which would lead to a policy recommendation, given the multiple factors that will need to be considered, but encouraged the development of a framework for decision making for discussion before the end of the programme. MPAC requested that a progress report be presented to MPAC at least annually.

- **Cardiotoxicity of antimalarials:** The Committee commended the ERG on the high quality of their report which was based on a thorough review of the literature related to the potential toxicity of antimalarials in both patients with malaria and in healthy subjects, with a particular emphasis on dihydro-artemisinin-piperazine (DHA+PQ). The Committee endorsed the conclusions of the ERG, noting the lack of evidence of a significant difference in the very low risk of cardiotoxicity following exposure to piperazine, chloroquine or amodiaquine, and that the very low risk of cardiotoxicity of piperazine-containing medicines are probably similar for healthy volunteers and malaria patients. MPAC also noted the need for special care in endemic areas of Latin America where malaria and Chagas disease coexist.
- **Surveillance, monitoring and evaluation operational manual:** The draft manual was well-received by MPAC and some suggestions were made on some areas for strengthening. MPAC agreed to provide an electronic review of the revised manual in June 2017 to facilitate a rapid release of the guidance.
- **Guidelines for malaria vector control:** MPAC is supportive of the consolidation of relevant malaria vector control guidance into one guideline in line with the evidence review process undertaken for the *Guidelines for the treatment of malaria*. These will be revised periodically as new evidence and recommendations become available.
- **Plasmodium knowlesi:** MPAC noted with concern the increase of *P. knowlesi* cases in Malaysia, potentially linked to a change in land use and the plausibility (though not definitively demonstrated) of human-vector-human transmission. If human-vector-human transmission is demonstrated in Malaysia, *P. knowlesi* would need to be considered a human malaria infection and elimination of *P. knowlesi* may be necessary for certification of malaria-free status.
- **Global Vector Control Response 2017–2030:** MPAC reasserted its support for raising global awareness of the importance of enhanced capacity and capability to improve vector control. MPAC noted that the document is high level and has been finalized and submitted in preparation for the World Health Assembly, but highlighted some key areas where advocacy and communication require refinement.
- **Online mapping tool for malaria vectors and parasites:** MPAC felt that the mapping tool could be useful to countries, but that the platform would be most useful if adapted to interface with DHIS2 and other national platforms for epidemiological data.
- **Strategic Advisory Group on malaria eradication:** MPAC members strongly supported the work of the SAG and endorsed the planned work packages with the advice to be mindful of the potentially broad scope and considerable overlap of the proposed work packages both across the SAG and with other efforts. Thus, suggesting the need to prioritize the potentially most urgent analyses such as risks to eradication and populations at future risk.
- **Framework for malaria elimination:** MPAC congratulated the secretariat and writing team, strongly endorsed the emphasis of a continuum from

high burden to elimination, and appreciated the challenge of developing a document that would be applicable to all settings.

- **Emergence and spread of multidrug resistant *Plasmodium falciparum* lineages in the Greater Mekong subregion:** MPAC endorsed the conclusions and recommendations of the ERG on multidrug resistant *P. falciparum* in the GMS including the critical need for surveillance outside the GMS to detect appearance of resistant parasites. As noted previously by MPAC, continued intensive regional malaria elimination efforts in the GMS remain a priority. Surveillance for *P. falciparum* resistance to artemisinin and partner drugs in the GMS is critical and should be continued and strengthened. Where surveillance signals a potential threat to leading ACTs, effective alternative ACTs should be identified and implemented before resistance reaches critical levels.
- **Situation update on *hrp2/3* gene deletions:** The report to MPAC was well received and the update on actions taken to address previous recommendations was appreciated. MPAC highlighted that although *hrp2/3* deletions are not an immediate threat to diagnosis in most places, it is critical to gather rapidly data to better map the areas that are impacted. MPAC requested regular updates as data become available and agreed to electronically review the global plan to address *hrp2/3* gene deletions when this is available.
- **Mass drug administration for malaria practical field manual:** The draft manual was well received by MPAC and the main issues raised were around the importance of clearly differentiating between the two main rationales for MDA, either as a morbidity/mortality reduction tool or as a transmission reduction tool in elimination settings.
- **Submicroscopic malaria infections:** MPAC members were supportive of the proposed evidence review on submicroscopic malaria infections and highlighted some specific areas for consideration, including the need to understand the contribution of submicroscopic infections to malaria transmission at different levels of transmission intensity. The review should also include evidence from the recent mass test and treat studies.
- **Overview of WHO policy recommendations for malaria vector control interventions:** MPAC noted that the draft information note it had been provided with was being revised to address feedback from the Vector Control Technical Expert Group. MPAC supported the planned expert advisory group meeting scheduled for 24–25 April 2017 to examine relevant trial designs for assessment of public health value of new vector control tools and that defining an intervention as “new” should be based on the mode of action and not chemistry. There was strong support for the potential use of catalytic funds from the Global Fund to support studies that will generate robust data on the public health value of potential new tools to support policy recommendations. MPAC supported the proposed re-convening of an evidence review group on PBO LLINs, scheduled for June 2017. It also considered the WHO pathway for new vector control tools and the transition from the WHO Pesticide Evaluation Scheme to pre-qualification. It was agreed that this process will be facilitated by strengthening the link between the VCAG and MPAC, with well-articulated roles and responsibilities for each.
- **Accelerating malaria elimination by 2020:** MPAC strongly endorsed the work package presented to support countries with the potential to eliminate by 2020 and highlighted the need for funding to take the work forward. MPAC indicated that it would like standing updates on the progress in malaria elimination at

least once per year and strongly supported establishing the global oversight committee and certification of elimination panel.

- **Global call for action to ensure universal access to malaria diagnosis and treatment:** There was wide support for this initiative and an acknowledgement that it should have been undertaken years ago. MPAC noted the importance of considering the broader health systems issues and how they can be taken into account when recommending a response.

## BACKGROUND

The WHO Global Malaria Programme (GMP) department convened the Malaria Policy Advisory Committee (MPAC) for its eleventh meeting in Geneva, Switzerland on 22–24 March 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 and ad hoc evidence review groups, whose work focuses on thematic areas and specific research questions to generate sufficient evidence to provide guidance. Over the course of the two-day meeting's open sessions, 15 MPAC members, five national malaria control programme managers, the WHO Secretariat and 57 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: an overview of highlights from the *World Malaria Report 2016* including the biological challenges posed by insecticide resistance and drug resistance, key activities and products of GMP since the last MPAC meeting, an update on work relating to malaria elimination and the discussion on eradication, highlights from the Partners Forum in the Greater Mekong subregion (GMS), summary results from a WHO multi-country evaluation of the implications of insecticide resistance for malaria vector control, an update on progress on the draft global vector control response, progress on activities for the RTS,S Malaria Vaccine Implementation Programme, and an update on the revitalization of the RBM Partnership, and concluded by welcoming the new CEO, Dr Kesete Admasu, as a standing observer to MPAC meetings.

## SUMMARY OF THE MPAC SESSIONS

### Update on RTS,S/AS01 Malaria Vaccine Implementation Programme

**Background:** In November 2016, the Global Fund to Fight AIDS, Tuberculosis and Malaria approved US\$ 15 million from its catalytic funds for the malaria vaccine pilots. Together with previous funding commitments made by Gavi, the Vaccine Alliance (up to US\$ 27.5 million, matching other sources 1:1) and UNITAID (US\$ 9.6 million), a total of US\$ 49.2 million has now been pledged for the first 4 years of the Programme

(2017–2020). These commitments enable initiation of the Programme in three countries at the scope and scale recommended by WHO. The vaccine will be deployed through routine health systems and observational studies used to evaluate (i) the feasibility of routine deployment of the four-dose vaccine regimen, (ii) consolidation of the safety profile of the vaccine, and (iii) evaluation of the vaccine's impact on survival. Intensive preparations are under way including:

- The selection of three countries in which the trial will be undertaken was made, and will be announced around World Malaria Day. Countries were selected based on responses from 10 ministries of health following a WHO call for expressions of interest to participate in the programme. Joint delegations from WHO, PATH and GlaxoSmithKline Biologicals (GSK) made initial visits to the countries in October–November 2016, where the countries' continued interest and suitability to participate in the pilot programme was confirmed.
- An advanced draft of the master protocol for the evaluation of the cluster-randomized pilot implementation was developed and was included in GSK's revised RTS,S Risk Management Plan, submitted to the European Medicines Agency in March 2017. The WHO Ethics Review Committee as well as relevant bodies in the three countries will subsequently conduct protocol reviews.
- WHO will release a Request for Proposals (RFP) to identify research partners to conduct the country evaluations. The successful applicants will lead the development of country-specific protocols for subsequent review by local ethics review committees.
- A collaboration agreement between WHO, PATH and GSK defining roles and responsibilities in the RTS,S Malaria Vaccine Implementation Programme is being finalized.
- To explore the potential for a joint regulatory review for the use of RTS,S in the pilots, representatives from the three pilot countries' national regulatory agencies convened in the context of the African Vaccine Regulatory Forum (AVAREF) on 18–19 February 2017.
- Preparation activities for vaccine introduction, regulatory approval, pharmacovigilance and evaluation readiness will continue over the course of this year, with the aim of starting implementation of the RTS,S malaria vaccine in pilot areas in 2018.

**MPAC conclusions:** MPAC congratulated GMP and partners on their efforts to obtain funding allowing the programme to go ahead. The committee was generally happy with the design of the programme and recognised the magnitude of the evaluation, which will involve approximately 720 000 children. It was noted that GSK will also conduct an observational, Phase 4 study of the vaccine's routine deployment in the same countries to obtain further pharmacovigilance data. The WHO evaluation team and GSK are working to maximise the complementarity of the two evaluations, which will not include the same children.

Questions were raised about the meaning of "implementability", one of the main end points. This refers largely to the ability to achieve high coverage with the fourth dose of RTS,S/AS01, an important end-point because of concerns over loss of protection against severe malaria if this dose is not given. GMP clarified that strenuous efforts will be made within the context of a national expanded programme on immunization (EPI) to ensure that the fourth dose is received by participating children. MPAC also suggested that the study measure the impact of including RTS,S in routine EPI on the incidence of other vaccine preventable diseases in intervention and non-intervention areas. The issue of what would happen to the comparison areas on completion of

the trial was raised; it was noted that this decision will be guided by the results of the evaluations. At this point, MPAC did not think it appropriate to articulate explicit criteria which would lead to a policy recommendation, given the multiple factors needing consideration, but encouraged the development of a framework for decision making for discussion before the end of the programme.

## Report back from the ERG on the cardiotoxicity of antimalarials

**Background:** The cardiotoxicity of antimalarial medicines has received renewed interest in recent years following the “Thorough QT” assessment of the dihydroartemisinin–piperazine formulation approved by the European Medicines Agency, which showed evidence of QT interval prolongation. Drug-induced QT/QTc interval prolongation is a surrogate indicator for increased risk of drug-induced torsade de pointes (TdP), a potentially lethal polymorphic ventricular tachycardia. Piperazine is a bisquinoline antimalarial that is structurally related to chloroquine. Many drugs among the quinoline and structurally-related medicines affect myocardial depolarization and repolarization, thus potentially prolonging the QT interval. WHO currently recommends the artemisinin-based combination treatment dihydroartemisinin–piperazine for the treatment of uncomplicated malaria.

To inform WHO recommendations, a group of experts met in October 2016 to review evidence on the cardiotoxicity risk of quinoline antimalarials and structurally-related medicines in people with and without clinical malaria. A summary of the ERG’s findings and proposed recommendations were considered by MPAC. These included:

- Apart from halofantrine, antimalarial medicines that prolong the QT/corrected QT (QTc) interval, such as quinine, chloroquine, artesunate–amodiaquine and dihydroartemisinin–piperazine, have been associated with a very low risk of cardiotoxicity.
- Risk factors for drug-induced QT/QTc prolongation include female gender, structural heart disease, genetic defects of cardiac ion channels, electrolyte disturbances, bradycardia, hepatic impairment, and concomitant use of medications that prolong the QT/QTc interval or increase drug levels. Antimalarial medicines that can induce QT/QTc interval prolongation should be used with caution in individuals with known heart disease, a family history of sudden unexplained death consistent with cardiac arrhythmias, or who are already taking medicines that can prolong the QT/QTc interval.
- Dihydroartemisinin–piperazine and artemether–lumefantrine have been the most intensively studied antimalarial drugs. No sudden deaths have been attributed to cardiotoxicity following artemether–lumefantrine. However, among ~200 000 treated individuals with close follow-up, one possible sudden cardiac death associated with dihydroartemisinin–piperazine administration has been reported. This finding is consistent with the risk of fatal cardiotoxicity associated with other QT/QTc-prolonging medicines in current use.
- Review of pharmacovigilance, clinical and preclinical data, along with preliminary results of PK/PD modelling, reveals no evidence of a significant difference in the risks of cardiotoxicity following exposure to piperazine, chloroquine or amodiaquine at the current recommended doses. The risks of cardiotoxicity of piperazine-containing medicines are probably similar for healthy volunteers and malaria patients.
- Drug-induced TdP and life-threatening ventricular tachyarrhythmias are very rare events, and there are no simple screening tests to identify people at risk. Further studies are needed to identify genetic polymorphisms and

other pre-existing conditions that may contribute to the risk of drug-induced cardiotoxicity. More evidence on the potential cardiotoxicity of chloroquine, amodiaquine and primaquine is needed.

**MPAC conclusions:** The Committee commended the ERG on the high quality of their report which was based on a thorough review of the literature related to the potential toxicity of antimalarials in both patients with malaria and in healthy subjects, with a particular emphasis on DHA-PQ. The cardiovascular toxicity of some antimalarials, such as acute hypotension induced by chloroquine when given by rapid infusion, was not covered by the review. It was noted that additional data on the cardiovascular toxicity of chloroquine may be available from the review of historical malaria-therapy studies. The committee noted that the review has demonstrated that DHA+PQ does increase the QTc interval in both patients with malaria and in healthy subjects in a very low proportion of cases, but is much less than the QT prolongation produced by halofantrine, which has a documented higher risk of death due to cardiotoxicity. The committee noted the report of one possible sudden cardiac death associated with dihydroartemisinin-piperaquine out of approximately 200 000 people treated at recommended doses. It noted that there are no screening tests to identify people at increased risk particularly during mass drug administration campaigns, i.e. subjects with an existing cardiac problem, congenital myocardial conduction defects, myocarditis due to Chagas diseases, or co-administration of drugs which are known to prolong the QTC.

## **Review of Surveillance, monitoring and evaluation. An operational manual**

**Background:** Surveillance is the continuous and systematic collection, analysis and interpretation of health data, and the use of those data in the planning, implementation and evaluation of public health practice. In elimination settings, malaria surveillance is designed for the identification, investigation and elimination of continuing transmission, the prevention and cure of infections, and the final substantiation of claimed elimination. Pillar 3 of the *Global technical strategy for malaria 2016–2030* (GTS) is the transformation of malaria surveillance into a core intervention in all malaria-endemic countries and in those countries that have eliminated malaria but remain susceptible to reintroduction of transmission.

The updated manual describes the general concepts and principles that govern malaria surveillance systems in all settings (Chapter 2). The manual also provides general guidelines for establishing a malaria surveillance system (Chapter 3), and outlines the recommended practices for recording, reporting, analysing and transforming data into information for action (Chapter 4). The following modifications and additions have been made to the two operational manuals for malaria surveillance for control and elimination settings previously published in 2012:

- the 2012 control and elimination operation manuals have been combined into a single document;
- the revised manual aligns with both the GTS and the *Framework for malaria elimination*, which was launched in 2017 – the framework includes the concept of a malaria elimination continuum and new methods for foci classification;
- new sections cover surveillance in the private and community health sectors, and migrant and mobile populations, and mapping of foci; and
- the case and foci investigation forms have been updated; a chapter on monitoring and evaluation of national malaria control programmes (NMCPs) and the GTS has been added.

**MPAC conclusions:** The draft manual was well-received by the MPAC and some suggestions were made on some areas for strengthening. Surveillance in migrant and mobile populations, border areas and other under-served populations that have poor access to case management is particularly challenging and it would be useful to provide more guidance or case studies as examples of how this can be done. MPAC requested that surveillance in the private sector receive additional attention, especially in elimination settings and that entomological surveillance be integrated throughout the manual as related to decision making rather than in a separate manual or just in one chapter. It will be important for the manual to articulate how it links to overall health systems and other data initiatives and it should not be seen as a stand-alone exercise. It was noted that there are many indicators and that there is a need to streamline and prioritize where possible from country input including detail on the use and interpretation of essential indicators. MPAC indicated a willingness to provide an electronic review of the revised manual in June to facilitate a rapid release of the guidance.

## Development of a Guideline for malaria vector control

**Background:** To guide the implementation of malaria vector control, GMP has identified the need to further review the scientific evidence base, and to update and consolidate the existing recommendations into a single document (WHO Guideline). The Guideline for malaria vector control will be part of an umbrella document on malaria prevention, together with the updated *Guidelines for the treatment of malaria*. The proposed Guideline for malaria vector control will follow the methods, processes and procedures for the development of WHO Guidelines to offer an analysis of the current evidence related to interventions for malaria vector control. A transparent and explicit process using the available evidence base will ensure the high quality of the Guideline. The analysis will inform and guide technical decisions, and provide a framework with which WHO Member States can develop specific malaria vector control guidelines.

The detailed objectives, target audience, scope and development processes of the Guideline were presented and endorsed at the last MPAC meeting (September 2016). Since then, the WHO Guideline Review Committee approved the development proposal (November 2016) and systematic reviews were commissioned by the Cochrane Infectious Disease Group at the Liverpool School of Tropical Medicine. It is anticipated that the Guideline will be finalized in February 2018.

**MPAC conclusions:** MPAC is supportive of the effort to consolidate all the malaria vector control guidance into one Guideline that follows the evidence review process supervised by the WHO Guidelines Review Committee similar to the *Guidelines for the treatment of malaria*. The Guidelines will make a clear differentiation between interventions for vector control (and thus community protection) and interventions that may provide only personal protection. MPAC highlighted the need to help countries to prioritize interventions given local contexts including elimination and the prevention of re-establishment of transmission, intervention impact and cost-effectiveness. Programme managers indicated that they receive requests for information on environmental management and on the impact of climate change. While it will not be possible to include environmental management, the impact of climate change or cost-effectiveness into this version of the Guideline, the online document will be revised periodically as new evidence and recommendations are available.

## Outcomes for the ERG on *Plasmodium knowlesi*

**Background:** At the September 2015 meeting, MPAC supported the constitution of an ERG to address the following knowledge gaps regarding *P. knowlesi*: the epidemiological distribution of *P. knowlesi* infection in humans; clinical outcomes; the range and distribution of the primary hosts and vectors; the most effective methods of control and prevention including diagnostics and treatment; the potential impact on malaria elimination and certification; the plausibility of human–vector–human transmission, potential future changes that may influence the levels of exposure; operational research priorities to limit *P. knowlesi* transmission to humans; and whether other primate malarias should be considered. The ERG noted that current evidence shows that *P. knowlesi* is still largely a zoonotic disease, but that it is not possible to exclude that human–vector–human transmission is taking place in some situations.

**MPAC conclusions:** MPAC noted with concern the increase of *P. knowlesi* cases in Malaysia, potentially linked to a change in land use which is increasing human exposure to vectors in forest areas and peri-urban areas colonised by the macaque hosts. Malaysia has declared a target of eliminating malaria by 2020, but needs guidance on whether elimination can be considered if *P. knowlesi* cases continue to be reported. If human–vector–human transmission is demonstrated in Malaysia, *P. knowlesi* would need to be considered a human malaria infection and elimination of *P. knowlesi* may be necessary for certification of malaria-free status. In terms of further understanding zoonotic versus human–mosquito–human transmission, MPAC suggested that GMP review the work that has been done on the classification of transmission for Avian Flu and Middle East Respiratory Syndrome (MERS) and report back.

## Update on the Global Vector Control Response 2017–2030

**Background:** Following the MPAC review of the draft global vector control response in September 2016, the document underwent an open online consultation and was reviewed by the WHO Executive Board (EB) in January. Support from the EB was overwhelmingly positive with constructive suggestions for further strengthening and a decision that the Secretariat should work in conjunction with interested Member States to develop a draft resolution for consideration at the World Health Assembly at their Seventieth session in May 2017. Following suggestions from the EB, the document was modified to adequately address: schistosomiasis; ethical considerations around vector control; changes in the WHO process for evaluation of new vector control products; approaches for multi-sectoral vector-borne disease control; coordination with WHO initiatives including the Health Emergencies Programme and International Health Regulations; a re-order of the pillars; and costing for implementation.

The approach to costing considered the estimated cost for full implementation of the priority activities for the interim period of 2012–2022, which mainly included staffing, surveillance and coordination costs, and excluded both the costs of vector control commodities and their deployment, as well as the costs of research and innovation on controlling vectors. A three-step approach was undertaken: 1) country categorization by historic risk, current burden, and number of major vector-borne diseases; 2) estimate of population at risk from at least one major vector-borne disease; and 3) estimate of resources required based on burden and/or per capita. The preliminary estimate of total cost for implementation is US\$ 330 million per year, with the caveat that accurate estimates of national resource requirements and costs will be developed through comprehensive national vector control needs assessments. GMP is currently developing a framework to guide these assessments.

**MPAC conclusions:** MPAC reasserted its support for raising global awareness on the importance of enhancing capacity and capability to improve vector control. MPAC noted that the document is high level and has been finalized and submitted in preparation for the World Health Assembly, but highlighted some key areas where advocacy and communication requires refinement. MPAC highlighted that although the document is about vector control response and does not include the costs of implementing disease-specific interventions, it however does propose vector-borne disease specific goals and it will be important that it is not viewed as over-promising, particularly given the low estimated cost of implementation of the vector control response. There were questions regarding the methodology on costing and an understanding that the real costing will have to be a bottom up process with support provided to countries. Finally, MPAC highlighted the need for leadership and a multi-sectoral approach at a local level, not just at the national level.

## Demonstration of online mapping tool for malaria vectors and parasites

**Background:** The GTS recognizes key biological challenges to achieving the targets and milestones for malaria control and elimination: vector insecticide resistance, *hrp2/3* gene deletions, and antimalarial drug efficacy and resistance. Geographical mapping technologies can be employed for rapid visualization and interpretation of complex data sets including temporal and spatial data series. Collection, analysis, publication and dissemination of data is a core part of WHO's mandate and a harmonized mapping tool that consolidates multiple data sets under the umbrella of biological threats was prioritized as a tool to inform country decision-making. A demonstration of the mapping tool was given and the Phase I (beta version) is projected for release by June 2017. Following consultations with countries and partners, the development will continue to a Phase II version later this year.

**MPAC conclusions:** The MPAC felt that the mapping tool could be useful to countries, but that the platform would be most useful if adapted to interface with DHIS2 and other national platforms for epidemiological data. It will also be important to ensure there is an indication of the difference between a lack of data availability versus data indicating no resistance or deletions.

## Update from the Strategic Advisory Group on malaria eradication

**Background:** GMP convened the inaugural meeting of the Strategic Advisory Group (SAG) on malaria eradication comprised of 13 leading experts across a variety of disciplines, supported by WHO Collaborating Centres and other key stakeholders on 29–30 August 2016 and the second meeting was held on 16–17 February 2017. In follow-up to the two key decision points from the SAG meeting in August, a position paper on malaria eradication was drafted and will be reviewed by the Executive Board in May to clarify WHO's long-term commitment to eradication. In parallel, the SAG will coordinate and direct a two-year scope of work to analyse future scenarios for malaria. Major discussion points of the February meeting included the discussion of work packages to improve the understanding of key determinants that will lead to malaria eradication, critical themes of costs and financing, the need to identify the components of health systems required for eradication, and management of expectations on when new tools will be available for deployment. The eight work packages are: economics of malaria eradication, health systems, high transmission areas, risks to eradication, populations potentially at risk in the future, community engagement, financing models, and lessons from previous elimination/eradication efforts. It has been noted that there are overlapping areas across the identified work

packages and that they will need to move forward in a harmonized fashion to ensure complementarity.

**MPAC conclusions:** MPAC Members strongly supported the work of the SAG and endorsed the planned work packages with the following advice: to be mindful of the potentially broad scope and considerable overlap of the proposed work packages both across the SAG and with other efforts (e.g. the malERA refresh exercise), and to prioritize the potentially most urgent analyses such as risks to eradication and populations at future risk. MPAC highlighted the importance of presenting a counterfactual case – the consequences of failing to eradicate – and stressed the importance of engaging actors from other sectors as soon and as fully as realistic. MPAC suggested engagement with the business sector to better integrate the economic benefits in endemic countries. It was clarified that the goal of this effort is not to develop an eradication plan and that the outcome is not predefined. Different products are planned for the eight work packages, though as work progresses and areas of overlap are identified, some work may be harmonized/ consolidated. An overall summary with recommendations will be published by the SAG.

## Finalization of the *Framework for malaria elimination*

**Background:** The *Framework for Malaria Elimination* based on three ERG meetings and multiple MPAC reviews has been finalized and was launched at a meeting of 21 malaria-eliminating countries in March 2017. The manual takes into consideration policy reviews and changes across all intervention areas (e.g. malaria prevention and treatment guidelines) since the previous manual (2007). Key changes and concepts include: the clarification of malaria terminology; the inclusion of all malaria transmission settings with a focus on low to zero transmission; indicative metrics for transmission intensity; illustrative intervention packages; simplified classification of foci; sub-national verification of elimination (country-led); and a revised process for WHO certification of (national) malaria elimination. The framework is available on the GMP website.

**MPAC conclusions:** MPAC congratulated the secretariat and writing team, strongly endorsed the emphasis of a continuum from high burden to elimination, and appreciated the challenge of developing a document that would be applicable to all settings. GMP confirmed that the framework would be updated on a continuing basis on-line to accommodate potential omissions and the accumulation of elimination science evidence, experience, and country perspectives. GMP advised that the graphic representation of the framework should not be interpreted as rigidly prescriptive and emphasized that the intention was to provide a conceptual guide to the more detailed text in subsequent chapters related to operational aspects, management and planning. MPAC advised that guidance on chemoprevention and prophylaxis be added explicitly at the next opportunity. There was a call for rapid translation of the document into relevant languages for malaria eliminating countries as well as translation into implementation guidance.

## Report on the ERG on the emergence and spread of multidrug resistant *Plasmodium falciparum* lineages in the Greater Mekong subregion

**Background:** At the request of MPAC and following the claim of the existence of new critical evidence, an ERG reviewed the evidence on the spread of multidrug-resistant *P. falciparum* in the GMS and the situation of artemisinin resistance outside the GMS. The regional and global risks this development poses to the efficacy of artemisinin-

based combination therapies were assessed in the context of contemporary and historical patterns of emergence and spread of drug-resistant malaria. Summary conclusions from the ERG were:

- Multiple instances of independent emergence and transnational spread of different lineages of artemisinin-resistant parasites have occurred throughout the GMS. One specific artemisinin-resistant lineage that is dominant at sites in western Cambodia, north-eastern Thailand and southern Lao People's Democratic Republic is also resistant to piperazine in western Cambodia and north-eastern Thailand but not present in other parts of the subregion such as Myanmar where artemisinin-based combination therapies (ACTs) continue to be highly effective.
- These multidrug-resistant parasites have been responsible for increasing dihydroartemisinin-piperazine failure rates across Cambodia over the last 5 years, rendering this important ACT mostly ineffective in affected areas. However, artesunate-mefloquine is currently efficacious in Cambodia, with cure rates >95%, and this combination is being used as first-line treatment in Cambodia.
- Parasites with genetic markers of artemisinin resistance have arisen independently at very low frequencies outside the GMS – including in Africa – for many years, but have not been associated with clinical delayed clearance. The most frequent allele observed in Africa is A578S which has not been associated with clinical or in vitro resistance to artemisinin. With the possible recent exception of Guyana, these parasites have remained at low frequencies and have not spread.
- The risk of a highly fit multidrug-resistant lineage spreading widely into higher transmission settings cannot be discounted; however, in the case of both artemisinin and piperazine multidrug resistance, this risk is mitigated by the likelihood that in higher transmission settings, host immunity, resistance and/or fitness mutations residing on different chromosomes are likely to be rapidly broken up by recombination in multiclonal infections.

Recommendations from the ERG are that: 1) the new data reaffirm the need for the GMS regional malaria elimination strategy to be fully implemented; 2) surveillance for artemisinin and partner drug resistance needs to be continued and strengthened in the GMS; 3) there is a critical need for surveillance outside the GMS to detect resistant parasites; and 4) where surveillance signals a potential threat to one of the leading ACTs, effective alternative ACTs should be identified and implemented before resistance reaches a critical level.

**MPAC conclusions:** MPAC strongly endorsed the conclusions and recommendations of the ERG on multidrug resistant *P. falciparum* in the GMS. As noted previously by MPAC, continued intensive regional malaria elimination efforts in the GMS are a priority. Surveillance for *P. falciparum* resistance to artemisinin and partner drugs in the GMS is critical and should be continued and strengthened. Additionally, while there is currently no evidence of artemisinin resistance outside the GMS it is important to strengthen existing surveillance networks by adding new sites, partners, and methods to detect such resistance, whether due to emergence or introduction and spread of resistant parasites. Lowered transmission intensity in parts of sub-Saharan Africa may increase the potential for the selection and spread of locally generated resistant strains. Where surveillance signals a potential threat to leading ACTs, effective alternative ACTs should be identified and implemented before resistance reaches critical levels.

Key research priority areas identified included: the mechanisms of artemisinin resistance; the relationship of population genetic structure to emergence/spread of

drug resistance; contribution of human mobility and antimalarial drug use behaviours to the spread of resistance; exploring alternative drug regimens; and assessing both the contribution of artemisinin resistance as well as partner drug resistance to the spread of multidrug-resistant parasites. MPAC also noted the importance of rational antimalarial treatment regimens including, if/when operationally feasible, rotation or use of a “mosaic” approach; understanding the potential role of military deployments for importation/spread of resistant parasites; understanding how antimalarial use/misuse in the private sector may contribute to promoting drug resistance; mapping drug resistance in relation to other factors to further explore issues that may be associated with its appearance/emergence; and monitoring parasite drug resistance patterns in returning travellers as a sentinel population.

## Situation update on *hrp2/3* gene deletions

**Background:** Since May 2016, GMP has published and updated an information note for the manufacturers, procurers and users of HRP2-based rapid diagnostic tests (RDTs) with interim guidance on how to investigate suspected false-negative RDT results, including *pfhrp2/3* gene deletions, and on alternative non-HRP2-based RDT options. In parallel, a technical consultation on *P. falciparum* *hrp2/3* gene deletions was held in Geneva on 7–8 July 2016. The final conclusions and recommendations from this consultation were presented to MPAC in September 2016. This situation update included a global review of reports on *hrp2/3* gene deletions, including the most recent reports from Uganda, Rwanda and Bangladesh and a progress report on actions since the last MPAC meeting.

**MPAC conclusions:** The report to MPAC was well received and the update on actions taken to address previous recommendations was appreciated. MPAC requested additional details concerning the methodological shortcomings of some of the reports which included selection of RDTs of unknown or poor quality for the initial investigations; failure to demonstrate amplification of single copy genes other than *hrp2/3*; and also suspicious sample quality issues due to prolonged storage in uncontrolled conditions. The decision to emphasize screening for deletions in symptomatic versus asymptomatic cases was questioned but the consensus was that identifying deletions in symptomatic cases was the first priority and that where resources permit testing in asymptomatic populations should be conducted. The assessment of secular trends, although currently very limited, could be of great utility in the future; at present, only Peru has such data available. It was noted that the majority of testing to date is on household survey samples and that more information is needed on symptomatic patients attending health facilities. MPAC noted that among the reference laboratories proposed to conduct *hrp2/3* gene deletion testing, only two are in malaria endemic countries (India and Cambodia) and none are located in Africa. Building lab capacity in Africa and other endemic countries is a priority when funding is available. In the interim, these reference labs have been identified because they have experience characterizing samples for *hrp2/3* genes as well as existing resources and capacity to begin rapidly testing samples. MPAC highlighted that although *hrp2/3* deletions are not an immediate threat to diagnosis in most places, it is critical to rapidly gather data to better map the areas that are affected. MPAC requested regular updates as data become available and agreed to electronically review the global action plan to address *hrp2/3* gene deletions when it is available.

## Mass drug administration for malaria. A practical field manual

**Background:** Currently, on the basis of the available evidence, WHO recommends mass drug administration (MDA): for interruption of transmission of falciparum malaria in areas approaching elimination, or as a morbidity and mortality reduction strategy during malaria epidemics and in exceptional complex emergencies.

For MDA to be successful, high coverage and adherence of the target population (i.e. > 80%) must be ensured, which require a high level of community engagement and participation. Door-to-door distribution is generally preferred to centralized distribution at a fixed site, and directly observed treatment (DOT), where feasible, is the best way to ensure adherence to treatment. Implementing MDA for malaria is a complex, logistically challenging operation that requires significant investments of resources (human, financial and logistic) as well as careful planning and organization. The manual provides technical and operational guidance on the practical aspects of organizing a successful MDA campaign for malaria including examples of useful tools used in the successful MDA campaign in Sierra Leone.

The key phases for efficient management are: design, planning and preparation, implementation, and monitoring and evaluation. Although these steps are common to all settings, the modalities of MDA implementation in different settings (urban versus rural, elimination versus emergency response) may differ. This manual is intended to provide general guidance based on successful experiences in malaria MDA, and should be adapted to local circumstances. The manual also provides tools, resources and templates for data collection and training that may be useful for developing tools for specific situations.

**MPAC conclusions:** The draft manual was well received by MPAC and the main discussions were on criteria for adoption of MDA rather than on the operational guidance included in the field manual. Particularly, the Committee emphasized two different purposes for the use of MDA: transmission reduction in areas close to elimination or as a tool to quickly reduce morbidity and mortality during emergencies or epidemics. MPAC noted that the risk benefit ratio associated with MDA may be different for each of the two purposes. In elimination situations where the risk of malaria infection and death is very low, even rare adverse events may raise concern. MPAC noted that it is important to provide precise guidance for selecting the antimalarial medicines taking into consideration the ACT being used as first line, the potential for misuse and the risks of severe adverse events, the occurrence of which could have negative impacts for malaria programmes and other programmes deploying MDA.

MPAC discussed and agreed that the list of medicines considered to be suitable for use in MDA efforts should be included in the manual. GMP committed to propose selection criteria for these choices, as well as articulating the risk benefit analysis (including considerations for pregnancy) for countries to consider in deciding which drug to use for MDA. MPAC also emphasized the need for programmes to specify the duration of MDA implementation and exit criteria for MDA programmes.

## Proposed ERG on submicroscopic malaria infections

**Background:** In recent years, the application of nucleic acid amplification (NAA)-based diagnostic tools in epidemiological surveys and research has expanded including the development of an ultra-sensitive RDTs with a limit of detection similar to NAA-based methods. Building on the findings and evidence gaps identified in 2013 by the evidence review on the role of molecular-based diagnostic techniques for malaria in low transmission areas, this review will consider new evidence on the natural history of submicroscopic infections, their contribution to malaria transmission, as well as case management and reporting once they have been detected. Where knowledge gaps still exist, the group will identify research priorities and propose study designs to evaluate the public health importance of submicroscopic infections and the impact of detecting them using highly sensitive diagnostic tests.

The proposed objectives of the evidence review group are:

- To review data on the natural history of submicroscopic *P. falciparum* and *P. vivax* infections in different epidemiological settings, to evaluate implications for detectability, duration of infection and to assess the relationship with symptoms of clinical malaria;
- To describe at the population level the contribution of submicroscopic *P. falciparum* and *P. vivax* infections to transmission with respect to different levels of vectorial capacity and immunity in the population;
- To define procedures for the case management and reporting of submicroscopic *P. falciparum* and *P. vivax* infections identified through multiple means, e.g., reactive case detection, surveys, research, etc.;
- To review and update the WHO recommendations on the diagnosis of *P. falciparum* and *P. vivax* malaria in low transmission settings, which were endorsed by MPAC in March 2014, based on the report of the 2013 ERG meeting;
- To establish a set of research priorities and study design characteristics to address knowledge gaps on the relative importance of submicroscopic infections.

**MPAC conclusions:** MPAC members were supportive of the proposed evidence review on submicroscopic malaria infections and highlighted some specific areas for consideration: the need to clearly evaluate the contribution of submicroscopic infections to malaria transmission at different levels of transmission intensity and how infectivity is measured. MPAC also noted that the review should include data from the mass test and treat studies, and the impact of submicroscopic infections on pregnancy outcomes. The consideration of serology as a surveillance tool was raised, but was considered beyond the scope of this ERG. It was highlighted that there are many unpublished studies that would be useful to include in the review if possible. Several MPAC members indicated an interest in joining the ERG meeting.

## Overview of WHO policy recommendations for malaria vector control interventions

**Background:** Vector control is an essential component of malaria prevention. GMP is responsible for developing policy recommendations for malaria vector control. As a precursor to policy development, the Vector Control Advisory Group (VCAG) assesses potential new tools, technologies and approaches and advises WHO on their potential public health value. Since its establishment, VCAG has reviewed numerous interventions covering a diverse range of entomological mechanisms of action and outcomes. Most of these had insufficient evidence of impact on malaria infection and/or disease; and do not currently have a WHO policy recommendation. The WHO process for evaluation of vector control products was presented and discussed.

The purpose of the proposed draft information note for MPAC review was to indicate which vector control interventions currently have a WHO policy recommendation for malaria prevention and control, as well as to indicate where existing policy recommendations may be extended to new vector control tools, and how this will affect the evaluation of tools that are presently being reviewed by WHO or are still under development. It was also explained that only those vector control products that belong to a product class or have a product claim for which there is a current WHO policy recommendation are eligible for WHO prequalification.

**MPAC conclusions:** MPAC felt that there was broad consensus on some of the major themes covered in the discussion of the draft information note: 1) the importance of using standardized definitions for terms such as product class, inferiority, equivalence, and public health impact; 2) that it will be critical to use the opportunity of a new evaluation process for vector control tools to link evidence on cost-effectiveness to the formulation of clear policy recommendations; and 3) that there is a need to define the appropriate level of evidence required to inform policy recommendations and to further explore the potential of using plausibility and non-randomized control trial data to assess the public health value of new interventions.

MPAC appreciated the feedback on the draft information note that was provided by the Vector Control Technical Expert Group (VCTEG), as well as plans for an expert advisory group convened on behalf of VCAG to develop a position statement on relevant trial designs for new vector control tools. MPAC emphasized the importance of the Trial Design expert advisory group to contemplate when randomized controlled trials are necessary and when other types of data collection could be used to inform evidence-based decisions, and to provide advice on trial design options to WHO via VCAG. In this context, MPAC suggested considering what types of studies will be possible in 5–15 years if significant reductions in transmission are achieved, and that defining thresholds for public health impact on disease and transmission levels might be helpful.

With regards to extending existing policy to new products currently being evaluated based on modes of action and not chemistry. MPAC suggested considering indoor residual spraying (IRS) products of equivalent or better entomological performance (based on similarity in mode of action) to current IRS formulations as having sufficient evidence to support their deployment (e.g., the mode of action being contact toxicity which is shared by all insecticides used in IRS, and not that insecticides in difference classes have different targets at the molecular level). MPAC agreed to electronically review a revised version of the information note so that it can be released before the next MPAC meeting. There was strong support for the proposed use of catalytic funds to support studies that would generate epidemiological impact data to inform policy decisions. MPAC supported the proposed evidence review on long-lasting insecticidal nets treated with a pyrethroid and piperonyl butoxide (PBO LLINs), scheduled for June 2017, and urged the VCAG to provide guidance rapidly on how to take these and other new products forward.

In addition to a request to revise the information note in line with VCTEG and MPAC advice, MPAC considered the WHO pathway for new vector control tools and the transition from the WHO Pesticide Evaluation Scheme to pre-qualification that has resulted in an uncertain path forward for specific products. It was agreed that this process will be facilitated by strengthening the link between the VCAG and MPAC, with well-articulated roles and responsibilities for each.

## **Malaria Elimination by 2020**

**Background:** GMP has established a unit to support malaria eliminating countries. The first subset of countries that the unit will focus on were highlighted in the WHO report *Eliminating malaria*, launched on World Malaria Day 2015, which identified 21 countries that had the potential to eliminate malaria by 2020. The analysis was based on the trend of indigenous malaria cases reported from 2000–2014, on the declared elimination objective of the country, and on expert opinion from the region. Key roles for WHO in support of countries to accelerate elimination include building on momentum generated by the countries, tracking progress, coordinating systematic efforts to accelerate country progress and the preparation for and certification of countries as malaria-free.

The framework proposed to help support malaria eliminating countries, starting at the country level include: 1) the recommendation for countries to form an independent national malaria elimination advisory committee to advise the national government on progress towards elimination and help prepare the country for the certification process; 2) the establishment of regional level progress reviews to ensure that milestones are met, that experiences are shared across countries and to promote cross-border collaboration; 3) the launch of a Global Forum to convene the malaria eliminating countries; and 4) the establishment of a global malaria elimination oversight committee to monitor progress, provide technical advice, identify risks to elimination, and recommend actions. The first Global Forum was launched with a meeting of the current 21 malaria eliminating countries on 16–17 February 2017.

**MPAC conclusions:** MPAC strongly endorsed the package of work that was presented in support of the malaria eliminating countries and highlighted the need for funding to take the work forward. MPAC indicated that it would like standing updates on the progress in malaria elimination at least once per year and provided strong support for establishing the global oversight committee and certification elimination panel. Critical capacities for the composition of the oversight committee include experience at the country level, experience from other disease elimination programmes, and representation from countries that have recently eliminated malaria. Capacity building at country level was highlighted as a key area for focus and important to maintain as the disease burden is reduced and elimination programmes are integrated into the health system. Also noted was the importance of continued identification of key operational research priorities. MPAC noted that the national committees should review data on health systems in addition to malaria epidemiological data and that maintaining national political will is critical.

## **Global call for action to ensure universal access to malaria diagnosis and treatment**

**Background:** Between 2000 and 2015, significant progress was made in extending the coverage of malaria diagnostic testing and treatment with appropriate antimalarial medicines. Despite this progress and although data are limited, current estimates suggest that large gaps in programme coverage remain. A better understanding as to why these gaps occur, who is affected by these gaps, and what strategies can be used to overcome them will help to ensure that there is universal access to care and that the targets outlined in the GTS are met.

The objectives of the global call to action are to: 1) characterize the access to and utilization of malaria diagnostic testing and treatment services at country level, and to identify bottlenecks in service; 2) identify particular population subgroups or risk factors associated with the gaps and the role played by the different delivery channels used to provide services; 3) review existing datasets and the methods used to estimate access to malaria diagnostic testing from routine health management information systems (HMIS) and from health facility and household surveys, and to provide clear methodological recommendations for strengthening the surveillance of malaria testing and treatment; and 4) identify effective strategies to increase the access to and use of diagnostic testing and treatment services, and to elaborate a global response plan. The work will include a literature review to summarise current access to malaria diagnosis and treatment, including major determinants and gaps; data analysis on the coverage of malaria diagnostic testing and treatment; and an economic analysis to look at increasing access to diagnostic testing and treatment.

These background papers will reflect important regional differences and will serve as the basis for developing a draft global action plan for mobilizing countries

and key stakeholders through a consultation including representatives of relevant ministry of health (MOH) programmes from multiple malaria-endemic countries and representatives of technical and funding agencies and nongovernmental organizations working with MOH programmes to improve access and reporting on malaria diagnostic and treatment services, including in the private sector and at the community level. The draft global action plan will be presented to MPAC in early 2018 for review and input.

**MPAC conclusions:** There was wide support for this initiative and an acknowledgement that it should have been undertaken years ago. MPAC noted the importance of considering the broader health systems issues and how they can be taken into account when recommending a response. The importance of not only improving access to diagnosis and treatment, but also ensuring that the results are reported through a strengthened routine surveillance system was highlighted. The methodological approach should consider distinguishing between broader health systems issues to be addressed and where much work has already been done from malaria-specific issues. Key issues include governance, integration of services compared to vertical programmes, cross-border issues, the ability to measure quality of care in addition to access to care, and working with the private sector. MPAC suggested close coordination with other groups that have worked on equity and access issues and looking at countries with good data to extrapolate lessons learned and distinguishing between high burden settings and elimination settings.

MPAC noted that although much of this meeting was concerned with elimination, achieving better control in the areas where malaria is still a major burden is of critical importance and that this initiative recognizes this fact.

All documentation related to this meeting can be found at: <http://www.who.int/malaria/mpac/mar2017/en/>

All previous MPAC meeting reports can be found here: [http://www.who.int/malaria/mpac/meeting\\_reports/en/](http://www.who.int/malaria/mpac/meeting_reports/en/)

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