Global **Malaria** Programme

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

World Health Organization

WHO/HTM/GMP/MPAC/2017.8

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-piperaquine (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 piperaquine, chloroquine or amodiaquine, and that the very low risk of cardiotoxicity of piperaquine-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 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-piperaquine 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. Piperaquine 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-piperaquine 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-piperaquine, 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-piperaquine 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-piperaquine 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 piperaquine, chloroquine or amodiaquine at the current recommended doses. The risks of cardiotoxicity of piperaquine-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