Global **Malaria** Programme

WHO Malaria Policy Advisory Committee (MPAC) meeting

SEPTEMBER 2016

MEETING REPORT

SUMMARY

On 14–16 September 2016, 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 nine sessions focused on: (1) an update on the RTS,S vaccine pilot implementation programme; (2) an update on the malaria elimination in the Greater Mekong subregion; (3) a review of *Malaria elimination: an operational manual*; (4) the results from a multi-country evaluation of the impact of insecticide resistance on malaria vector control; (5) an update on the Strategic Advisory Group on malaria eradication; (6) an update on the development of guidelines for malaria vector control; (7) the development of the Global Vector Control Response; (8) a proposed evidence review group to consider the cardiotoxicity of antimalarial medicines; (9) a report on the WHO technical consultation on detection and surveillance of HRP2/HRP3 deletions; (10) recommendations for the surveillance, monitoring and evaluation taskforce; (11) a proposed evidence review group to review *Plasmodium knowlesi*; (12) the proposed target product profile for ivermectin; and (13) proposed plans for the *World Malaria Report*.

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

- **RTS,S vaccine:** MPAC reiterated the urgent need to launch the RTS,S pilot implementation projects as per the November 2015 joint SAGE–MPAC recommendation, including an assessment of the impact on mortality. Neither the design nor the sample size should be changed. MPAC urged GMP and partners to vigorously pursue ways to cover the current funding shortfall and agreed on a statement to highlight the importance of the pilot projects.

World Health Organization

- **Malaria elimination in the Greater Mekong subregion:** MPAC noted the progress that is being made in the region. In response to a comment that there is new evidence indicating that partner drug resistance is being driven by artemisinin resistance and that a few multidrug resistant parasite lineages are outcompeting the other *P. falciparum* parasites and spreading geographically. WHO called for the submission of the new evidence, which will be quickly reviewed. The assessment of the relevance of the information, and the potential implications will be reported back to MPAC.

- ***Malaria elimination: an operational manual:*** MPAC concluded that the manual is comprehensive, and has incorporates several new elements based on the growing evidence base is a valuable update to the previous manual; additional suggestions were provided to improve clarity.

- **Results of the Impact of Insecticide Resistance Project:** MPAC highlighted that the study findings reaffirm the key public health role that pyrethroid impregnated long lasting insecticidal nets continue to play in the face of emerging insecticide resistance and support the current WHO recommendations in accordance with GPIRM, and do not indicate a need for changes to current policy. However, MPAC reiterated the need to re-evaluate the evidence base periodically and reaffirmed the urgent need to continue research into, and development, of new classes of insecticides and new tools for vector control to effectively manage insecticide resistance.

- **Strategic Advisory Group on malaria eradication:** MPAC supported the two key decisions of the SAG meeting: 1) to develop a position statement that clarifies the current terminology and confirms WHO's commitment to long-term malaria eradication, and 2) to undertake analyses to provide advice to WHO on the determinants, expected cost, timeframe, and potential future strategies for malaria eradication over the ensuing decades.

- **Malaria vector control guidelines:** MPAC noted that there are a number of documents for vector control and supported the harmonization and preparation of an evidence-based document using the formal WHO process including external review.

- **Global Vector Control Response:** MPAC commended the progress in the development of the GVCR over an abbreviated timeframe and highlighted the need for disease control and vector experts to work more closely together across diseases and to ensure the meaningful inclusion of non-health sectors.

- **Cardiotoxicity of antimalarial medicines:** MPAC strongly supported the convening of the ERG to review the cardiotoxicity of quinoline antimalarial medicines and the proposed list of experts suggested.

- **Detection and surveillance of HRP2/HRP3 deletions:** MPAC noted the serious threat posed by these gene deletions and appreciated the update on the situation. MPAC broadly agreed with the recommendations from the WHO consultation, and urged GMP to monitor closely the possible spread of these parasites given the strong selective pressure that the deletion would impose and to develop a plan of action for surveillance and response that can be supported by partners and implemented in countries.

- **Surveillance, monitoring and evaluation taskforce recommendations:** MPAC noted that the collection and analysis of the proposed indicators is essential for country and global monitoring and provided proposed additional indicators, while noting that only essential data should be collected.

- **Evidence review group on *Plasmodium knowlesi*:** MPAC strongly supported the proposed ERG on *P. knowlesi* and suggested expanding the scope to include other primate malarias which may naturally infect humans – notably *P. cynomolgi*.

- **Ivermectin target product profile:** MPAC made several suggestions on the proposed target product profile including the need to define "significant reduction", to assess the feasibility of defining a measurement of effect in vectors as an interim endpoint, to make the target product profile generic rather than exclusively for ivermectin, to characterize biologically active metabolites that may explain prolonged endectocidal activity, and that weekly dosage is not operationally feasible based on current MDA experience. MPAC will review the revised profile electronically.

- ***World Malaria Report*:** MPAC supported keeping a hard copy version of the *World Malaria Report* as a useful reference, and making the country profiles online only. MPAC cautioned that access to Internet remains a barrier in many parts of the world but agreed that it would be useful to enhance the contents in the online version.

BACKGROUND

The WHO Global Malaria Programme (GMP) department convened the Malaria Policy Advisory Committee (MPAC) for its tenth meeting in Geneva, Switzerland on 14–16 September 2016. 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 in order to generate sufficient evidence to provide guidance. Over the course of the two-day meeting's open sessions, 13 MPAC members, four national malaria control programme managers, the WHO Secretariat and 53 observers discussed the updates and progress in the areas of work 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 general updates on the work of the WHO-GMP units: Entomology and Vector Control; Prevention, Diagnostics and Treatment; Strategy, Evidence and Economics; Surveillance, Monitoring and Evaluation; and Technical Support and Capacity Building. In addition, he presented key messages from findings from WHO's *Eliminating malaria* report, including the significant increase in the number of countries with very low number of cases reported annually since 2000 and the identification of 21 countries with the potential to eliminate local transmission by 2020. The Director highlighted critical areas of work including the effort to develop a Global Vector Control Response in collaboration with the Department of Neglected Tropical Diseases and the Special Training Programme for Research and Training in Tropical Diseases; work to better understand coverage gaps in diagnostic testing and treatment and how to address them; highlights from the Greater Mekong subregion; and the work of the newly established Strategic Advisory Group on malaria eradication.

SUMMARY OF THE MPAC SESSIONS

Update on RTS,S/AS01 vaccine pilot implementation programme

Background: The Initiative for Vaccine Research (IVR) and GMP provided an update on progress with the RTS,S pilot implementation including an update on the country selection, study design, engagement with PATH and GSK, integration of Phase IV studies and pilot implementation, and funding commitments. There is currently a critical funding gap after commitments from GAVI and UNITAID. The consequences of not proceeding with the pilots after the EMA positive opinion and WHO recommendation will be serious for the development of malaria and other vaccines targeted at low income countries in the future to meet public health needs in low-income countries.

MPAC conclusions: MPAC supported the efforts made by GMP and IVR to move towards launching the pilot implementation by liaising and planning with the partners involved. MPAC reiterated the strong support for the WHO recommendation on the pilot implementation based on a (i) comprehensive, thorough scientific evaluation, (ii) a WHO recommendation, and (iii) a positive opinion from the European Medicines Agency (EMA). MPAC strongly opposes any reduction in the scope of the planned studies, the sample size or in the number of countries in response to resource limitations as it considers that this would seriously undermine the rationale for, and scientific integrity of the pilot implementation. MPAC urged GMP and partners to urgently consider options to cover the funding shortfall as upcoming decision points for several partners puts the pilot implementation at risk. Finally, MPAC observed that a failure to move towards the recommended pilot implementation despite the mandate from SAGE and MPAC, two global health advisory bodies, also reflects a fundamental gap in the public health funding architecture to support pilot implementation of new interventions developed exclusively for low-income countries, after obtaining regulatory and policy approval. MPAC recommended that a communications strategy be developed to raise public awareness on this issue and suggested a separate communication from the MPAC to the WHO Director General.

Update on malaria elimination in the Greater Mekong subregion post Emergency Response to Artemisinin Resistance

Background: Based on the *Strategy for malaria elimination in the Greater Mekong subregion* (GMS), with the goal of eliminating malaria by 2030 (*P. falciparum* malaria by 2025), the former Emergency Response to Artemisinin Resistance (ERAR) hub together with the WHO Regional Offices for South-East Asia and the Western Pacific and other partners have supported countries in the subregion to develop national strategies for elimination. At the end of 2016, the ERAR hub will transition from containment to elimination and provide support for capacity building and technical collaboration, cross border collaboration, monitoring product quality, priority research, surveillance and monitoring and evaluation, and coordination and governance. Insecticide resistance monitoring indicates no evidence of resistance in *An. dirus* throughout the GMS and no evidence of vector resistance in Myanmar and Thailand. Resistance to DDT has been identified in Lao People's Democratic Republic and some pyrethroid resistance has been identified in Viet Nam and Cambodia. Summary results from molecular studies with Kelch 13 (K13) have confirmed that artemisinin resistance has emerged independently in all countries of the GMS; therapeutic efficacy studies indicate that the majority of cases that have delayed parasite clearance still clear their infections provided that the artemisinin combination therapy (ACT) partner drug remains effective, even in areas of high prevalence of K13 mutants; and the declining number of cases in some study sites requires a longer study period to meet

the required number of study participants. Monthly monitoring in all countries shows a trend of declining cases compared to 2015, although key policy and implementation challenges remain.

MPAC conclusions: MPAC noted the progress that is being made in the region and asked what more should be done. The current analysis from the regional experts is that with the Global Fund commitments, lack of funding is not the constraint to accelerating progress. Insufficient political commitment to action and country leadership were identified as the limiting factors. Other aspects of the programme which could be improved are cross-border collaboration, health systems strengthening and the need for more data to indicate if insecticide resistance is an urgent issue for the region. Some on the committee called for urgent action, commenting that new evidence suggests that partner drug resistance is being driven by artemisinin resistance and that a few multidrug resistant parasite lineages are outcompeting the other *P. falciparum* parasites and spreading geographically. WHO called for the submission of the new evidence, which will be quickly reviewed. The assessment of the relevance of the information, and the potential implications will be reported back to MPAC.

Review of *Malaria elimination: an operational manual*

Background: The 13-member Evidence Review Group was first convened in September 2015 and has met three times to support the development of the revised *Malaria elimination: an operational manual.* An advanced draft was shared with MPAC for input before the document is further circulated to national malaria control programme managers and finalized for publication. Key new elements in the manual compared to the 2007 version include: all levels of malaria transmission are included instead of only moderate and low endemic settings; programme actions are highlighted across the continuum of transmission from high to no transmission; the critical role of information systems and surveillance as an intervention is emphasized; both rapid diagnostic tests (RDTs) and light microscopy are recommended for malaria diagnosis; focus classification has been simplified to three instead of seven types; the proposed process for certification is simplified; and a proposed threshold for the potential for re-establishment of transmission. MPAC was asked to comment on the overall content, in addition to providing specific inputs on malaria terminology; the continuum of transmission; diagnostic testing in elimination settings; and the revised WHO certification process.

MPAC conclusions: MPAC concluded that the manual is comprehensive and has captured much needed and long awaited updates to the previous manual such as revisiting the foci classification, including RDTs in the diagnostic tool kit, and others. The revised manual also addresses countries through the entire range of transmission and not only those with low or moderate transmission intensity, consistent with the Global Technical Strategy. However, MPAC cautioned that in its current form, the manual risks confusing countries by implying that they should abandon their malaria control strategies and re-plan for a goal of elimination regardless of the current level of transmission. It was suggested that the document could be more concise by including a summary in the beginning of every chapter and placing more descriptive material in annexes. MPAC members will send additional comments on the manual electronically.

Results of the Impact of Insecticide Resistance Project

Background: Major gains have been made against malaria in recent years, largely through the substantial scale-up of insecticidal interventions targeting *Anopheles* mosquitoes including long-lasting insecticidal nets (LLINS) and indoor residual spraying (IRS). However, their effectiveness is threatened by widespread resistance

to insecticides. Efforts to manage this threat, in line with the WHO *Global plan for insecticide resistance management in malaria vectors* (GPIRM, 2012), have been restricted by numerous factors including the dearth of evidence linking resistance to decreased vector control effectiveness. To address this absence of evidence, a multi-country evaluation was undertaken in Benin, Cameroon, India, Kenya and Sudan from 2009 to 2016, coordinated by WHO. This represents the first initiative to assemble a large data set of connected entomological and epidemiological observations to provide quantitative insights on the implications of insecticide resistance on malaria vector control effectiveness across different transmission settings. Key conclusions from the study were that there was: 1) strong evidence that LLINs provide personal protection against malaria across all the study areas; 2) no detectable evidence of a difference in LLIN personal protection effectiveness between areas with either higher or lower pyrethroid resistance; 3) some evidence of loss of community protection in higher resistance clusters 4) no evidence of an increase in malaria disease burden associated with higher levels of pyrethroid resistance; and 5) a possible trend of increasing resistance across some of the evaluation areas. Further conclusions were that in one area of Sudan with pyrethroid resistance but bendiocarb susceptibility, 1) adding deltamethrin IRS to LLINs provided no additional protection whereas adding bendiocarb IRS to LLINs almost halved malaria incidence relative to LLINs alone and 2) that carbamate IRS in addition to LLINs appeared to slow the emergence of pyrethroid resistance relative to LLINs only. It was noted that insecticide resistance was highly labile between years and showed marked heterogeneity on a relatively fine scale, which indicates the need for improved phenotypic tests and has implications for sentinel site monitoring. Publication of country-specific results in peer reviewed journals is ongoing, and final consolidated outcomes will be presented at a Symposium at the American Society of Tropical Medicine & Hygiene (ASTMH) 65th annual meeting in November 2016 and followed by a summary publication.

MPAC conclusions: MPAC supported the conclusion that the data indicate that LLINs are still providing personal protection working across a range of levels of pyrethroid resistance, although the evaluation areas did not represent areas with of the high levels of resistance as seen, for example, in West Africa. MPAC cautioned that the analyses showing some evidence of the loss of community protection could be due to confounding as the study, by definition, could not be fully randomized. Further studies may be required to verify this finding. MPAC also noted that limited data are available on vector behaviour from the evaluation area which may have been useful in interpreting the study outcomes. MPAC highlighted that the study findings support the current WHO recommendations in accordance with GPIRM, and do not indicate a need for changes to current policy. However, MPAC noted that this study was descriptive rather than a randomized trial and that the results should be treated with caution. MPAC also reiterated the need to re-evaluate the evidence base periodically and reaffirmed the urgent need to continue research into, and development of, new classes of insecticides and new tools for vector control to effectively manage insecticide resistance.

Strategic Advisory Group on malaria eradication meeting outputs

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. Invited speakers addressed the lessons learned from previous eradication efforts on smallpox and polio and SAG members presented potential key determinants of malaria eradication including economic development; poverty; population growth, movement and dynamics; and urbanization. The SAG agreed that although malaria eradication is epidemiologically feasible, it is likely not technically

possible with the current tools; that research and innovation must continue and will drive the effort; and that WHO needs to lead the eradication debate and reaffirm the commitment to malaria eradication while explicitly NOT launching an eradication campaign. The two key decision points from the SAG meeting were: 1) a position paper on malaria eradication should be presented to the Executive Board in January that clarifies WHO's long-term commitment to eradication and 2) in parallel, the SAG will coordinate and direct a two-year scope of work to analyse future scenarios for malaria, taking into consideration a broad set of biological, technical, socioeconomic, political and environmental determinants, including potential products of innovation. Based on these analyses, the SAG will provide advice to WHO on the timeframe, expected cost and potential strategies of malaria eradication over the ensuing decades.

MPAC conclusions: MPAC noted that there is confusion regarding the WHO position on malaria eradication. While the goal has always been a world free from malaria as articulated in the Global Technical Strategy, that does not imply a time bound, fully financed malaria eradication campaign. MPAC supported the two key decisions of the SAG meeting: 1) to develop a position statement that clarifies the current terminology and confirms WHO's commitment to long-term malaria eradication, and 2) to undertake analyses to provide advice to WHO on the determinants, expected cost, timeframe, and potential strategies for malaria eradication over the ensuing decades.

Development of malaria vector control guidelines

Background: GMP is in the process of developing consolidated vector control guidelines to 1) provide global evidence-based recommendations on vector control strategies and tools for malaria control and elimination, and 2) provide a framework for the development of specific and more detailed national vector control strategies and protocols, promoting the use of effective malaria control measures at the national level based on the best available evidence. Key topics that will be covered in the guidelines include: core malaria control interventions, complementary vector control interventions, issues and challenges in implementation, vector control by eco-epidemiological settings, vector control under special circumstances, and new tools and methods for malaria vector control. The development is guided by an internal WHO Steering Group, a Guideline Development Group (Vector Control Technical Expert Group), and an external review group. The guidelines are anticipated to be launched by the end of 2017.

MPAC conclusions: MPAC noted that there are a number of documents for vector control and supported the harmonization and preparation of an evidence-based document using the formal WHO process including external review. MPAC further noted that the timelines are ambitious and cautioned that the rate limiting factor may be the availability of evidence based data and the review process. The guidelines will need to include aspects related to safety, resistance, quality assurance, pregnancy, and the combination of interventions. Guidelines for post-elimination settings should be included without using the term "scaling-back." MPAC suggested engaging malaria programme managers and partners to ensure that the guidelines meet their needs.

Development of the Global Vector Control Response

Background: Vector-borne diseases account for 22% of the estimated global burden of all infectious diseases and the world has recently witnessed a significant re-emergence of vector-borne diseases. Although impressive global reductions in malaria have been attributable in large part to the massive scale-up of LLINs and

IRS, a critical lack of human, infrastructural and financial capacity has hampered sustained and successful vector control more broadly. Following support expressed by Member States at the Sixty-ninth World Health Assembly and the 139th meeting of the Executive Board, the WHO Secretariat was requested to develop a Global Vector Control Response (GVCR). This development process is co-led by the Global Malaria Programme, the Department of Control of Neglected Tropical Diseases, and the Special Programme for Research and Training in Tropical Diseases, and is supported by a Steering Committee. An advanced draft of the GVCR will be discussed by the WHO Executive Board at their 140th meeting. The vision of the draft GVCR is a world free of vector-borne diseases that affect humans and the goal is to reduce the burden and threat of vector-borne diseases through sustainable, effective vector control. The draft objectives of the response are: to strengthen vector control as a key strategy for vector-borne disease reduction and prevention, including environmental management in urban and rural development initiatives; to establish and enhance intersectoral collaboration for integrated action; to develop locally adaptive systems for efficient vector surveillance and control; to enhance and link entomological and epidemiological evidence in order to optimize the planning and implementation of vector control; and to ensure government and partner commitment to vector control through legislation, policy and planning. The Response currently comprises four pillars: 1) inter-and intra-sectoral action and collaboration; 2) enhanced entomological surveillance, and vector control monitoring and evaluation; 3) scale-up and integration of tools/approaches; and 4) community engagement and mobilization. It is based on a foundation that will enhance human, infrastructural and health systems capacity; adapt programmatic systems, structure, and policies and improve regulatory and normative support; increase basic and implementation research and innovation; and enhanced advocacy, resource mobilization and coordination of partner support. An electronic version of the Response will be shared with MPAC for comment before submission to the Executive Board in October 2016.

MPAC conclusions: MPAC commended the progress in the development of the GVCR over an abbreviated timeframe. Key areas of discussion were that the development of entomology career avenues are required to inspire young entomologists and that public health teaching courses should include an entomology component. MPAC felt that non-entomology leadership should be sensitized and vector control success stories (e.g. LLINs scale-up to reduce malaria) can be used to raise the visibility of vector control and the need to strengthen the vector control component of national programmes for maximum impact. There is a need for disease control and vector experts to work more closely together across diseases and to ensure the meaningful inclusion of non-health sectors. MPAC will provide comments on the next draft electronically.

Proposed evidence review group on cardiotoxicity of antimalarial medicines