WHO Malaria Policy Advisory Committee (MPAC) meeting

MARCH 2016

MEETING REPORT

SUMMARY

On 16–17 March 2016, the WHO Malaria Policy Advisory Committee (MPAC) convened to review updates and progress with respect to specific thematic areas of work carried out by the Global Malaria Programme (GMP).

The meeting included 11 sessions focused on: (1) the RTS,S vaccine pilot implementation programme; (2) new WHO guidelines for iron supplementation; (3) drug efficacy and response; (4) the establishment of a Strategic Advisory Group on malaria eradication; (5) long-lasting insecticidal nets (LLINs) treated with a pyrethroid insecticide and piperonyl butoxide; (6) changing WHO procurement criteria for malaria rapid diagnostic tests (RDTs); (7) a proposed Evidence Review Group to review quality control methods for RDTs; (8) a WHO consultation to develop preferred product characteristics of ivermectin for malaria transmission control; (9) progress on elimination efforts in the Greater Mekong Subregion; (10) an update from the Evidence Review Group on elimination; and (11) the communication of MPAC meeting outcomes and resolutions.

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

- **RTS,S vaccine:** MPAC emphasized the importance of mobilizing the necessary funding to support the RTS,S pilot implementation projects and strongly endorsed the efforts made by the Initiative for Vaccine Research (IVR) and GMP in this regard.
- **Iron supplementation guidelines:** MPAC welcomed the new WHO guidelines based on a well-conducted evidence review. The review clarified long-standing questions regarding the impact of iron supplementation on children living in malaria-endemic areas and the guidelines provide an important and helpful resource.



- **Drug efficacy and response:** MPAC endorsed the Technical Expert Group's recommendations that molecular surveillance be used to guide the routine assessment of the effectiveness of intermittent preventive treatment in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP). MPAC also agreed, that IPTp-SP remains associated with improved birth outcomes in almost all places in sub-Saharan Africa, irrespective of SP's failure to clear or prevent parasitaemia. MPAC supported the conclusion that it is not harmful to give IPTp-SP to women living in the few areas with sextuple dhfr/dhps mutant genotype. Furthermore, MPAC agreed that it is important to protect the partner drugs in artemisinin-based combination therapies (ACT), as resistance to the partner drug is as important as artemisinin resistance for the efficacy of the combination.
- **Strategic Advisory Group on malaria eradication:** MPAC members stressed the importance of developing a good communications strategy that outlines how this advisory group will function so as to distinguish it from ongoing or planned malaria elimination efforts and national programme strategies.
- **Long-lasting insecticidal nets:** There was a general consensus among MPAC members that the evidence review group report on long-lasting insecticidal nets treated with a pyrethroid and piperonyl butoxide was comprehensive and proposed sound recommendations based on the evidence available. As emerging evidence becomes available, it will be important to specify whether pilot implementation studies should be based on entomological or epidemiological endpoints.
- **WHO procurement criteria:** While there was consensus among MPAC members to support the transition of the rapid diagnostic test (RDT) product testing programme to prequalification, the Committee highlighted the need to be cautious in setting timelines in order to ensure that there is no detrimental impact on the supply chain.
- **Quality control for RDTs:** MPAC supported the convening of an evidence review group on this topic, and emphasized the need for WHO to map the magnitude of HRP2 deletions and to develop a communications strategy for the dissemination of key information on this emerging public health issue.
- Elimination in the Greater Mekong Subregion: MPAC noted the excellent progress made towards elimination in this subregion and identified the clear need for funding in order to sustain momentum. The importance of country ownership in elimination efforts was highlighted.
- **Ivermectin for malaria transmission control:** MPAC supported GMP's plans to convene a meeting together with the Department of Neglected Tropical Diseases (NTDs) to review available evidence and to define a target product profile for ivermectin as a potential tool to reduce or block malaria transmission.
- **Update of the Evidence Review Group on elimination:** MPAC was updated on the development of *Malaria elimination: an operational manual*, which focuses on the progression of all malaria-endemic countries towards elimination. The manual will be formally reviewed at the September 2016 MPAC meeting. MPAC stressed the importance of country programmes conducting parallel reviews.
- **MPAC communications:** There was general agreement that only one report communicating the key outcomes from MPAC meetings was required, and members expressed a preference for the report's continued publication in the Malaria Journal.

BACKGROUND

The WHO Global Malaria Programme (GMP) department convened the Malaria Policy Advisory Committee (MPAC) for its ninth meeting in Geneva, Switzerland on 16–17 March 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, 14 MPAC members, five national malaria control programme managers, the GMP team and 40 observers discussed the updates and progress in the areas of work presented. Recommendations were discussed in the final closed session.

UPDATES FROM THE GLOBAL MALARIA PROGRAMME

The GMP Director opened the meeting by providing general updates on the work of the WHO-GMP units: Prevention, Diagnostics and Treatment; Drug Efficacy and Response; Strategy, Evidence and Economics; Entomology and Vector Control; and the new unit on Technical Support and Capacity Building. In addition, he provided a summary of key findings from the *World Malaria Report 2015*. These findings included the unprecedented decline in the malaria burden between 2000 and 2015, with an estimated 37% decrease in global malaria case incidence and a 60% decline in malaria mortality rates. Additional updates were provided on the transition of the Roll Back Malaria Partnership; recent WHO-GMP products; plans to scale up implementation of rectal artesunate; plans for multi-agency efforts to scale up IPTp; work with UNITAID and the Innovative Vector Control Consortium to support access to new generation vector control products; progress on bringing innovation to impact in vector control; and GMP's engagement in WHO's response to Zika. He also provided a list of anticipated expert consultations and guidance documents planned for 2016.

MPAC conclusions: In the closed session, MPAC discussed the update on rectal artesunate and supported the efforts of GMP and the Medicines for Malaria Venture to conduct well-designed pilot implementations of rectal artesunate suppositories for pre-referral treatment of severe febrile illness in children at the community level. The discussion highlighted the risk of promoting a monotherapy versus the potential life-saving ability of rectal artesunate when applied correctly for pre-referral treatment. Ensuring clear communication of the importance of the referral and the need for a full treatment course of an ACT after rectal artesunate is of critical importance.

SUMMARY OF THE MPAC SESSIONS

Update on RTS,S/AS01 vaccine pilot implementation programme

Background: In a meeting held in October 2015, MPAC and the Strategic Advisory Group of Experts on Immunisation (SAGE) jointly recommended that RTS,S be evaluated in pilot implementations before wider introduction at the country level is considered. The critical issue is the extent to which the protection demonstrated in children aged 5–17 months in the Phase 3 trial can be replicated in the context of routine health systems, particularly in light of the need for a 4-dose schedule that requires new immunization contacts. Based on these recommendations, WHO convened a consultation in January 2016 to develop the design of the pilot implementation studies using the 4-dose schedule in three to five distinct epidemiological settings at the subnational level in sub-Saharan Africa, covering moderate-to-high transmission settings. WHO is now working with interested countries, partners and donors to finalize the design of the pilot implementation programme and to mobilize financial support for these pilots.

MPAC conclusions: MPAC welcomed the progress report provided by the IVR and GMP on the position paper published by WHO in January and the planning under way to design and mobilize resources to support the pilot implementation. It was agreed that both SAGE and MPAC will be kept informed of the progress of the pilots on a regular basis, as recommended in the joint MPAC-SAGE session in October 2015.

WHO guidelines for iron supplementation

Background: The recently published WHO guidelines on *Daily iron supplementation in infants and children* (based on evidence from a recently published Cochrane systematic review¹) were presented by the WHO Department of Nutrition for Health and Development. While it is widely known that children living in malaria-endemic areas are at high risk for iron-deficiency anaemia, iron supplementation was previously believed to potentially increase the risk of malaria. The review evaluated the effects and safety of iron supplementation, with or without folic acid, in children living in areas with malaria transmission. It concluded that iron treatment does not increase the risk of clinical malaria when regular malaria prevention or curative services are provided. The new WHO guidelines recommend that, in malaria-endemic areas, the provision of iron supplementation in infants and children be carried out in conjunction with public health measures to prevent, diagnose and treat malaria.

MPAC conclusions: MPAC members commended the high quality of the evidence review and the new WHO guidelines in addressing an issue that has hampered iron supplementation in malaria-endemic areas for over a decade.

Drug Efficacy and Response Technical Expert Group

Background: The fourth Drug Efficacy and Response Technical Expert Group (TEG) discussed three topics: (1) an update on artemisinin resistance; (2) monitoring the efficacy and effectiveness of preventive treatment, including intermittent preventive treatment in pregnancy with sulfadoxine-pyrimethamine (IPTp-SP) and seasonal malaria chemoprevention (SMC); and (3) the prevention and treatment of multidrugresistant malaria. The TEG concluded that the tools currently available are sufficient to detect artemisinin resistance, but new tools that take into account the lag phase and tail in the parasite clearance curve should also be evaluated. The TEG also defined a series of new criteria for suspected and confirmed artemisinin resistance. The detection of artemisinin resistance signifies an epidemiological threat, but it may not be associated with reduced ACT efficacy. In monitoring the efficacy and effectiveness of preventive treatment, the TEG concluded that, in almost all places in sub-Saharan Africa at a population level, IPTp-SP is associated with improved birth outcomes, irrespective of SP's failure to clear or prevent parasitaemia. The presence of parasites bearing the sextuple mutant haplotype containing Pfdhps A581G at a prevalence of >35% appears to negate the benefits of IPTp-SP for birth outcomes. However, the evidence suggests that even in these circumstances, it is not harmful to give IPTp-SP to women with the sextuple mutant. The places in sub-Saharan Africa with the sextuple mutation appear to be few and geographically limited. For national malaria control programme (NMCP) settings, molecular surveillance could be used to monitor IPTp-SP effectiveness, as it is more feasible than in-vivo protocols (assessing the clearance of parasitaemia) and delivery protocols (assessing the change in pregnancy outcomes). Standardized protocols have been developed to conduct molecular surveillance to monitor IPTp-SP. The TEG discussed the optimal protocol with which to monitor drug resistance in areas where SMC is being implemented under the ongoing ACCESS-SMC. With regard to the prevention and treatment of multidrug-resistant malaria, the TEG discussed extended treatments and triple therapies. According to a modelling study presented, the TEG noted that, in areas where there is no established multidrug resistance, the simultaneous deployment of multiple effective ACT first-line treatments may help to delay the emergence of drug resistance.

MPAC conclusions: MPAC endorsed the TEG's recommendations that molecular surveillance be used to guide the routine assessment of IPTp-SP effectiveness, and noted that even in areas of high resistance, IPTp-SP is effective. **MPAC agreed that it is critical to protect the partner drugs in ACTs**, as resistance to the partner drug is as important as artemisinin resistance for the efficacy of the combination.

Update on convening a Strategic Advisory Group on malaria eradication

Background: The GMP Director provided an update to MPAC on the establishment of a Strategic Advisory Group on malaria eradication (SAG), which is expected to be convened in June. Building on the goals and targets set by the WHO *Global Technical Strategy for Malaria 2016–2030*, adopted by the World Health Assembly in May 2015, and in the context of the Sustainable Development Goals, the malaria eradication SAG will advise WHO on the feasibility, potential strategies and cost of eradicating malaria over the coming decades. After the introduction of the terms of reference for the malaria eradication SAG, all meeting participants broke into smaller groups to discuss and provide input on the questions the SAG should answer, the minimum set of conditions and tools to consider if eradication is possible, the full list of determinants of future malaria trends that should be considered, and the structure of the final report. The groups reported back after the breakout session, and the feedback will be incorporated into the establishment of the malaria eradication SAG.

MPAC conclusions: MPAC members agreed that the breakout sessions were useful in providing significant input from both the members of the committee and the other participants in order to finalize the terms of reference for the SAG on malaria eradication. MPAC also stressed the importance of defining a clear communications strategy in order to distinguish the work of this group in considering the future eradication of malaria from the ongoing work to update the guidance on malaria elimination and prevention of reintroduction for countries achieving malaria-free status.

Update on long-lasting insecticidal nets treated with a pyrethroid insecticide and piperonyl butoxide

Background: Long-lasting insecticidal nets (LLINs) treated with a pyrethroid insecticide and the synergist piperonyl butoxide (PBO) have become available. Three of these nets have a WHO Pesticide Evaluation Scheme (WHOPES) interim recommendation as LLINs. Two of these nets are now undergoing WHOPES Phase III evaluation to inform a decision on giving full recommendation for their use. Following previous advice by MPAC (March 2015), GMP established an independent Evidence Review Group (ERG) to review the available evidence with the objective of identifying areas and conditions under which PBO nets could be deployed. The ERG found that, while PBO LLINs appear to have an increased efficacy in certain settings (areas where the principal vectors exhibit metabolic resistance to pyrethroids), the evidence is not yet sufficient to justify a complete switch from pyrethroid-only LLINs to PBO LLINs across all settings. Furthermore, there is currently no evidence to assume higher efficacy or greater utility as a resistance-management strategy across all settings. The ERG recommended that PBO LLINs be used only where universal coverage with effective vector control of populations at risk of malaria will not be reduced, as PBO LLINs may be more expensive than standard LLINs. Due to the potential for an antagonistic effect between PBO and organophosphates, PBO LLINs should not be used in areas programmed for IRS with pirimiphos-methyl CS. In order to build the evidence base, ERG provided guidance on where pilot implementation with robust evaluation should be carried out and specified that the recommendations would be revised periodically on the basis of emerging evidence.

MPAC conclusions: The MPAC supported the conclusions and recommendations by WHO arising from the ERG. On the basis of the current evidence, MPAC cautioned that it will be important to specify whether pilot implementation studies should be based on entomological or epidemiological endpoints.

Changing WHO procurement criteria for malaria rapid diagnostic tests

Background: Since 2010, WHO's guidance for malaria rapid diagnostic test (RDT) procurement has been based on the performance results of the WHO Product Testing Programme. By evaluating RDTs and sharing results with buyers, the programme has shifted the malaria RDT market share to well-performing products and dramatically expanded access to diagnostic testing. WHO is now considering prequalification as a requirement for procurement. WHO prequalification involves a review of a product dossier and inspection of the manufacturing site(s), in addition to an independent performance evaluation by Product Testing. The goal of universal access to diagnosis requires quality-assured products, as well as a healthy market. Therefore, before adopting the new criteria for WHO prequalification, GMP commissioned an independent assessment of the potential impact of this policy change on RDT quality, supply security and affordability. Analyses of the market and the WHO prequalification (PQ) pipeline suggest that a phased transition to WHO pregualification for malaria RDTs by the end of 2017 would be beneficial, as it would provide an incentive for manufacturers to invest in processes to ensure quality, and enable consumers to distinguish between products produced by manufacturers that have invested in strong quality management systems. To mitigate some of the risks identified, the transition should be phased: for P. falciparum-only RDTs where there are already five prequalified products, the shift to WHO PQ could be implemented as proposed; for both the P. falciparum -pan or P. falciparum /P. vivax combination RDTs, for which

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