Global **Malaria** Programme

WHO Malaria Policy Advisory Committee (MPAC) meeting

APRIL 2019

MEETING REPORT

SUMMARY

On 10–12 April 2019, the World Health Organization (WHO) Malaria Policy Advisory Committee (MPAC) convened to review updates and progress in malaria control and elimination, and to provide guidance on specific thematic areas of work carried out by the Global Malaria Programme (GMP).

The meeting's eight sessions focused on 11 topics including: 7 updates for guidance (the "High burden to high impact" approach; malaria elimination in the Greater Mekong Subregion; the Strategic Advisory Group on malaria eradication; the GMP policy-making and dissemination process; the Evidence Review Group on mass drug administration; the Malaria Elimination Oversight Committee and STOP-Malaria; the outcome of the technical consultation on external competence assessment for malaria microscopy); 2 updates for information (drug efficacy and resistance; and the Evidence Review Group on malariogenic potential); one update for approval (the RTS,S Malaria Vaccine Implementation Programme and framework for decision-making); and one new process for approval (prioritization of new topics for policy recommendation development).

The key conclusions of MPAC included:

- **"High burden to high impact" (HBHI) approach:** MPAC commended the work of the national malaria control programmes (Ministries of Health) and WHO and partners in support of countries to implement a coordinated response to accelerate progress against malaria. The discussion highlighted the need to move away from short-term technical assistance towards long-term capacity-building, which needs to be embedded in all elements of the approach.

- **RTS,S malaria vaccine implementation and decision-making framework:** MPAC endorsed the proposed "Framework for Policy Decision on RTS,S/AS01 Malaria Vaccine", noting that the timing of

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the suggested analysis will be based on the accumulation of events, currently expected approximately 24 months after introduction. Following MPAC endorsement, the framework is now fully approved by both advisory bodies.

- **Drug efficacy and resistance:** MPAC appreciated the update and noted that the presence of mutants for resistance to artemisinin identified in countries such as Guyana and Papua New Guinea, among others, did not spread from the Greater Mekong Subregion. MPAC noted with concern the issue of poor quality of dihydroartemisinin-piperaquine (DHA-PIP) being used in Africa, with a particular focus on the stability of the DHA component. MPAC requested that WHO propose a course of action to improve the availability of prequalified DHA-PIP to address this urgent risk of spreading resistance.

- **Elimination in the Greater Mekong Subregion:** MPAC noted the considerable progress in the subregion and commended countries, regional offices, and the Mekong Malaria Elimination Programme. The discussion emphasized the continued importance of cross-border collaboration, including collaboration on the regional data-sharing platform, forest malaria, and mobile and migrant populations. MPAC encouraged continued attention to developing and testing specific interventions for resident and transient forest goers, including chemoprophylaxis.

- **Strategic Advisory Group on malaria eradication (SAGme):** MPAC commended the SAGme on its continued progress towards completing its charge and compiling the work packages, acknowledging the important ways forward that have been identified. There was considerable discussion on the conclusion by the SAGme that megatrends favour eradication and concern that this conclusion may be based on the current relationships between malaria transmission and factors like urbanization and climate change. It was noted that these relationships are likely to change over time as vectors adapt to urbanisation, a trend already observed in Africa, and the invasion of vectors into new geographic areas (including *An. stephensi* into Africa and Sri Lanka).

- **GMP policy-making and dissemination:** MPAC congratulated GMP on improvements to its policy-making and dissemination processes. MPAC welcomed the improved coordination between the WHO Prequalification Team and GMP to reduce timelines, and suggested that formalized scientific advice should include written documentation on the performance criteria and evidence required. MPAC noted that the pre-read documentation and presentation were oriented around potential new products and that it will be important to ensure that the proposed policy pathway also facilitates the development of policy recommendations for new strategies that are agnostic of product. The Committee highlighted the need for global guidance to be flexible enough to enable countries to target resources where they are most needed, as well as the importance of ensuring country input into the entire policy-making process.

- **Prioritization of new topics for policy recommendation development:** MPAC appreciated GMP's efforts to be more transparent and inclusive in prioritizing the topics for the development of policy guidance and highlighted the need to ensure that country and regional voices are heard. Furthermore, MPAC recognized the differential prioritization of guidance needs in the different regions and asked GMP to propose a strategy to address this issue. MPAC also suggested that criteria for prioritization would be useful, recognizing that capacity and resources are limited.

- **Evidence Review Group (ERG) on mass drug administration (MDA):** MPAC appreciated the work of the ERG and agreed that in this transition period, the MDA recommendations should follow the process and methodology of the WHO Guidelines Review Committee and new GMP Guideline Development Group (GDG). As a result, recommendations listed in the ERG report are not endorsed by MPAC and will be resubmitted for approval by MPAC after full policy recommendation process has been completed.

- **ERG on malariogenic potential:** MPAC welcomed the results of the ERG on malariogenic potential and acknowledged that the work will need to continue as new data become available.

- **Malaria Elimination Oversight Committee (MEOC) and STOP-Malaria:** MPAC appreciated the work of the MEOC and the countries that are on track to meet the 2020 elimination milestone of the *Global Technical Strategy for Malaria 2016-2030* (GTS). MPAC called on GMP to convene a technical consultation on zoonotic malaria to examine the biology, transmission, classification and implications for control and elimination. The proposed STOP-Malaria pilot programme was strongly endorsed by MPAC. There was a suggestion to consider expanding the programme to HBHI countries, but it was also acknowledged that the technical expertise and skills required in high malaria transmission settings are quite different from those developed in the successful STOP-Polio model.

- **External competence assessment for malaria microscopy consultation:** MPAC endorsed the external competence assessment of the malaria microscopy programme and suggested that GMP invest in an e-learning platform to support training in addition to competence assessment.

BACKGROUND

The WHO Global Malaria Programme (GMP) convened the Malaria Policy Advisory Committee (MPAC) for its 15th meeting in Geneva, Switzerland on 10–12 April 2019. MPAC convenes twice annually in Geneva to provide independent strategic advice to WHO on policy recommendations for malaria control and elimination. Over the course of the two-day meeting's open sessions, 13 MPAC members, four national malaria control programme managers, the WHO Secretariat and over 40 observers discussed the updates and progress in the work areas presented. Conclusions and recommendations to GMP were discussed in the final closed session of the Committee on day three.

The meeting participants were reminded of the procedures governing WHO's assessment of MPAC members' declarations of interest. It was noted that the GMP Secretariat requested and received feedback from all the experts present at the meeting regarding their declarations of interest. The following members disclosed various interests: Professor Graham Brown, Professor Thomas Burkot, Professor Gabriel Carrasquilla, Professor Umberto D'Alessandro, Professor Abdoulaye Djimde, Professor Azra Ghani, Dr Caroline Jones, Professor Patrick Kachur, and Dr Dyann Wirth. The GMP Secretariat reviewed the disclosures and determined that there were no conflicts of interest with respect to the topics for decision at this meeting.

UPDATES FROM THE GLOBAL MALARIA PROGRAMME

The GMP Director opened the meeting by reminding participants that the malaria-endemic world is becoming increasingly divided into two distinct groups: high-burden countries and countries close to elimination; and that while the world is likely to meet the 2020 elimination milestones of the GTS, it is unlikely to meet the morbidity and mortality targets. He provided a brief summary of the data from the *World Malaria Report 2018* and highlighted the "High burden to high impact" (HBHI) approach, which was launched by WHO and the RBM Partnership to End Malaria at the end of 2018 to support countries with a high malaria burden (HBHI was discussed in detail in Session 2). Other updates provided by the Director included the progress made by malaria eliminating countries supported by the E-2020 initiative, progress in the Greater Mekong Subregion (GMS), updates from the Strategic Advisory Group on malaria eradication (SAGme), highlights of the work on policy-making, the imminent start of the Malaria Vaccine Implementation Programme (MVIP), and key meetings and documents launched since the last meeting.

SUMMARY OF THE MPAC SESSIONS

Update on the "High burden to high impact" approach

Background: The HBHI approach is a targeted malaria response that aims to reaffirm commitment and refocus activities initially in the highest burden countries to accelerate progress towards the GTS goals through four response elements: political will, strategic information, better guidance for more targeted and efficient use of resources for optimal impact and coordinated response. Building on a foundation of effective health systems and a multisectoral response, these four mutually reinforcing response elements will support the implementation of prioritized operational plans derived from evidence-informed national malaria strategic plans. In the 10 highest burden countries of Africa, national governments are convening a broad array of global and national partners to kick-start their country-led approach. The process has already started in Uganda and Nigeria, pioneering the way forward for other countries to learn from their experiences.

Representatives from Nigeria, Uganda and India presented key updates from their national programmes and examples of using the HBHI response elements to help accelerate progress with coordinated support from partners. In Uganda, commitment from all levels of the political system is translating into appropriate actions. The President has called for the establishment of a national malaria fund, and civil society has been mobilized to contribute to the Mass Action Against Malaria initiative. In Nigeria, a high-level National Malaria Dialogue is planned for July 2019 to establish increased political responsibility at national and state levels to allocate appropriate levels of domestic funding. India reported 3 million fewer cases in 2017, achieving a 24% reduction compared to 2016. The presentation demonstrated that India's programme had identified the ingredients necessary to drive down malaria, including strong national leadership and funding, a coordinated response to malaria, a high level of political commitment and the use of strategic information to stratify districts for adequate response. India's success will provide an example for other countries to follow.

MPAC discussion: MPAC commended the work of the national malaria control programmes (Ministries of Health) and WHO and partners in supporting countries to implement a coordinated response to accelerate progress against malaria. The Committee recognized the value of meaningfully engaging civil society and

empowering communities, but cautioned that this should be done to increase ownership. MPAC noted the need to actively engage academia to ensure that national technical expertise and locally applicable knowledge are used more effectively. MPAC noted that the HBHI approach provides an opportunity to share best practices and to learn from other country experiences. The India experience demonstrates the value of the four response elements, which, when modified to suit the local context, will be applicable to African countries.

MPAC noted that while countries can achieve greater impact with existing tools and resources, achieving elimination will likely require the introduction of new tools. Such new tools should be evidence-based and available to underserved populations. The discussion highlighted the need to move away from short-term technical assistance towards long-term capacity-building, which will need to be embedded in all elements of the approach. MPAC raised the importance of countries sharing their data and information to facilitate planning and cross-border collaboration. MPAC noted the risk of trying to address too many priorities at once, but recognized that the full value of the HBHI approach will be accrued by taking forward all four interdependent and mutually reinforcing response elements in parallel.

Update on the RTS,S Malaria Vaccine Implementation Programme (MVIP) and Framework for Policy Decision

Background: The MVIP was developed in response to the 2016 WHO recommendation to pilot implementation of the RTS,S/AS01 malaria vaccine. The MVIP is supporting the introduction of the malaria vaccine in selected areas of Ghana, Kenya and Malawi, as well as the evaluation of the programmatic feasibility of delivering a four-dose schedule, the vaccine's impact on mortality, and its safety in the context of routine use. The primary aim of the Programme is to address outstanding questions related to the public health use of the RTS,S/AS01 malaria vaccine in order to enable a WHO policy decision on the broader use of the vaccine in sub-Saharan Africa. The Programme is jointly coordinated by GMP, the Immunization, Vaccines & Biologicals (IVB) Department and the WHO Regional Office for Africa, in close collaboration with other WHO departments and country offices, ministries of health in pilot countries, PATH and other partners. Introduction of the malaria vaccine is country-led and was launched in April 2019.

A Working Group was established, including representatives from the WHO advisory bodies involved in the policy review that led to the 2016 WHO malaria vaccine position paper. The Working Group reviewed the data and information that had emerged since the 2016 decision and developed the "Framework for Policy Decision" document to present to WHO's Strategic Advisory Group of Experts (SAGE) on Immunization and MPAC. The Framework provides recommendations on how the data generated by the MVIP can be used to inform WHO policy decisions as such data become available. The Framework provides an opportunity for discussion and alignment prior to key time points for SAGE's and MPAC's recommendations to WHO on the broader use of RTS,S/AS01. The following points represent a summary of the Working Group's recommendations:

1. The SAGE and MPAC should consider recommending a step-wise approach for reviewing and making policy decisions on the broader use of RTS,S/AS01 based on emerging pilot data.

    Step 1: A WHO policy recommendation on the use of RTS,S/AS01 beyond the pilot countries could be made if and when:

    i. concerns regarding the safety signals observed in the Phase III trial (related to meningitis, cerebral malaria and sex-specific mortality) are

satisfactorily resolved by demonstrating either a lack of a significant risk during RTS,S/AS01 pilot implementation or an assessment of a positive risk–benefit profile despite adverse event(s); and

ii. either severe malaria or mortality data trends are assessed as *consistent with a beneficial impact* of the vaccine;

Based on current assumptions across the three MVIP countries related to the expected rate of accumulating events and the timing of vaccine introduction, the required data on safety and impact trends could be available approximately 24 months after RTS,S/AS01 vaccine introduction in the Programme. Once there are preliminary data on event rates, updated estimates can be confirmed within a statistical analysis plan.

Step 2: Adjustments or refinements to the policy recommendation for broader use of RTS,S/AS01 can be made based on the final MVIP dataset, with particular focus on the value of the fourth dose. This final dataset is expected to be available approximately 50 months after the start of vaccination in the third MVIP country.

2. There is a need to resolve safety concerns over meningitis, cerebral malaria and sex-specific mortality to establish the risk–benefit profile of the vaccine, as reassuring safety data are required for a policy recommendation.

3. The policy recommendation for broader use could be made in the absence of data showing a vaccine impact on mortality. Impact on severe malaria is an acceptable interim surrogate indicator for impact on mortality to support a policy recommendation if assessed as consistent with a beneficial impact.

4. A policy recommendation for broader use of RTS,S/AS01 need not be predicated on attaining high coverage (including coverage of the fourth dose). For a newly introduced vaccine, high coverage is frequently not attained until several years after the start of implementation.

5. Barring substantial adverse impact on the coverage of other vaccines or malaria control interventions, the impact of RTS,S/AS01 introduction on the coverage of other vaccines or malaria control interventions will not be major factors influencing a vaccine recommendation. Rather, these indicators should inform strategies for implementation, including opportunities for improvement.

6. Cost-effectiveness estimates should be regularly refined as data become available for increasingly precise calculations and presented at appropriate time points.

7. Expansion within MVIP countries should be synchronized with the recommendation for broader use across sub-Saharan Africa.

8. In the context of the step-wise approach to policy recommendations, the pilots should complete the data collection to establish the public health value of the fourth dose and assess the vaccine's impact on mortality.

9. Conflicting data among the MVIP countries would require careful investigation into the reasons for such differences. The pilots should continue with plans for analysis, even if data are delayed or not available in all countries.

10. Criteria are suggested that could result in WHO not making a recommendation for use of the RTS,S/AS01 vaccine in routine immunization programmes or that may lead to a decision to defer a policy recommendation to a later time point.

The Framework was endorsed by SAGE during its meeting on 3 April 2019 which was attended by the MPAC chair with other MPAC members participating electronically. The chair of SAGE participated in the MPAC session by phone.

MPAC conclusions: MPAC endorsed the proposed "Framework for Policy Decision on RTS,S/AS01 Malaria Vaccine", noting that the timing of the suggested analysis will be based on the accumulation of events, currently expected approximately 24 months after introduction. MPAC suggested that the framework document be more concise and that background information should be moved to an accompanying annex. MPAC was informed that an analytical plan is being developed to describe how and when the analyses will be conducted during the course of the pilot including data from household surveys, and community and hospital surveillance systems. Household surveys will inform Information, Education and Communication (IEC) and other mechanisms to address any potential reductions in malaria control interventions that might occur as a consequence of the vaccine implementation. MPAC agreed with the importance of addressing this potential risk, but felt that it should not preclude a recommendation to proceed with implementation if the safety and impact data are supportive. MPAC reinforced the importance of collecting incremental cost-effectiveness data to inform decisions about potential further deployment. Following MPAC endorsement, the framework is now fully approved by both advisory bodies.

Update on drug efficacy and resistance

Background: The situation of antimalarial drug efficacy and resistance focused on special cases. The session included updates on definitions, partial artemisinin resistance, case reports, piperaquine resistance in Africa and advice on data sharing, methods to assess the origin of parasites, the quality control of circulating dihydroartemisinin-piperaquine (DHA-PIP) and marketing of artemisinin-piperaquine. Key definitions included:

- Antimalarial resistance: the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject;
- Multidrug resistance (MDR): resistance to more than two antimalarial compounds of different chemical classes; usually referring to *P. falciparum* resistance to chloroquine, sulfadoxine-pyrimethamine, and a third antimalarial compound; and
- Artemisinin resistance: delayed parasite clearance following treatment with an artesunate monotherapy or with an artemisinin-based combination therapy (ACT); partial resistance would be more appropriate wording.

Reports of partial artemisinin resistance in Guyana, Papua New Guinea, India, Equatorial Guinea, Rwanda and the Horn of Africa were discussed. It is important for investigators reporting resistance to use consistent definitions and to share data with WHO for confirmation. Different methodologies are used to assess the origin of parasites; it would be useful to standardize the minimum information needed to confirm the origin of resistant parasites before publishing findings. Where WHO has investigated, results indicate de novo emergence and potential clonal expansion.

Currently, one DHA-PIP product is prequalified (and another is under evaluation). However, this product is difficult to procure, leaving many generic, non-prequalified compounds of varying quality available on the market. DHA is unstable at temperatures above 30°C, in humid conditions and when in contact with partner medicines. This results in treatment that is effectively piperaquine monotherapy, leading to selection

of resistant parasites; infections with increased copy numbers of *Pfplasmepsin2-3*, a molecular marker of piperaquine resistance, have been detected in some African countries. There is an urgent need to support quality control of the generic DHA-PIP compounds circulating in Africa and discourage the use of non-prequalified products such as artemisinin-piperaquine.

MPAC conclusions: MPAC appreciated the update and noted that the presence of mutants for resistance to artemisinin identified in countries such as Guyana and Papua New Guinea, among others, was not the result of spread from the GMS but arose independently. Key questions raised during the session were on the need for investigators and countries to share information with WHO on a potential public health concern; the need for methodologies to identify the origin of resistant parasites; the need to identify if other potential mechanisms in addition to *Pfkelch13* are involved in artemisinin resistance; and the need to consider the half-life of a drug when evaluating the drug efficacy of an ACT.

MPAC noted with concern the issue on the quality of DHA-PIP used in Africa, with a particular focus on the stability of the DHA component. It was noted that there is a lack of availability of WHO prequalified product and that many countries are procuring non-prequalified products. MPAC requested that WHO propose a course of action to improve the availability of prequalified DHA-PIP to address this urgent risk of spreading resistance.

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

Background: Countries of the GMS are accelerating towards their shared goal of malaria elimination by 2030. The six countries – Cambodia, China (specifically Yunnan Province), the Lao People's Democratic Republic (PDR), Myanmar, Thailand and Viet Nam – have achieved remarkable progress. Between 2012 and 2017, the reported number of malaria cases fell by 75% and malaria deaths by 93%. In 2018, the total estimated cases in the GMS remained the same (1% decline) compared to the previous year. Cases are mostly concentrated in a few provinces of Cambodia, Lao PDR and Viet Nam. The number of *P. vivax* cases increased by 32% compared to 2017, while countries made significant progress towards *P. falciparum* elimination, particularly Cambodia (26% decline), Myanmar (34% decline) and Thailand (39% decline), and China reached zero locally transmitted malaria cases in 2017. The remaining challenges include inadequate case management among high-risk populations (e.g., forest goers in remote areas), delays in rolling out radical treatment for *P. vivax* malaria, low utilization of insecticide-treated nets (ITNs), and increased population movement into areas of active transmission.