

# WHO Malaria Policy Advisory Group (MPAG) meeting

OCTOBER 2021

MEETING REPORT

## SUMMARY

On 4–7 October 2021, the World Health Organization (WHO) Malaria Policy Advisory Group (MPAG) convened virtually to review updates and progress, and to provide guidance on thematic areas of work by the Global Malaria Programme.

The virtual meeting focused on eight topics in five open sessions: 1) “Rethinking Malaria”; 2) update on the technical consultation on non-inferiority evaluations of vector control tools; 3) a discussion on malaria rebound; 4) an update on antimalarial drug resistance in Africa; 5) an update on rectal artesunate (RAS) and quality of care; 6) a review of the relationship between chemoprevention and drug resistance; 7) an update on the *WHO guidelines for malaria (1)*; and 8) a joint session with the Strategic Advisory Group of Experts on Immunization (SAGE) to review the evidence and consider a recommendation for broader use of the malaria vaccine.

The key conclusions of MPAG to the Global Malaria Programme included:

- **“Rethinking Malaria”:** MPAG members were highly supportive of the conclusions so far and highlighted the importance of making this a “whole of government and whole of society” approach. MPAG suggested that the rethinking malaria process should include an in-depth critical analysis of the current situation at the national and even subnational level to identify specific elements to be changed in each context. The importance of strengthening effective partnerships between academics and implementers was also emphasized. An action plan needs to be drafted, ensuring that malaria is part of universal health coverage and enhancing the mobilization of domestic resources.
- **Non-inferiority evaluations of vector control tools:** MPAG commended WHO for the cross-departmental work on this important issue and

adopted the proposed approach for non-inferiority evaluation of vector control tools, along with the other detailed recommendations made in the meeting report.

- **Malaria rebound:** Members were very supportive of the need for this review, as there are implications for individuals who may be at risk following a targeted intervention that impairs the development or maintenance of clinical immunity, as well as for communities at risk of epidemic malaria following a malaria-free period. Members noted the importance of understanding the disease burden in populations and level of clinical immunity prior to the intervention; seasonality; age-associated change in risk; duration of the intervention; and nature of health services in the follow-up period.
- **Antimalarial drug resistance in Africa:** MPAG requested that the Global Malaria Programme develop a regional response plan to address the threat of artemisinin partial resistance, highlighting that investment is urgently needed to support this response. MPAG recommended conducting high-quality efficacy surveillance, systematically incorporating tools such as molecular markers and where possible ex vivo tests to confirm the emergence of resistance to key partner drugs. In addition, the Group asked the Global Malaria Programme to explore options to tackle the potential risk of reduced efficacy of the partner drugs within the artemisinin-based combinations.
- **Rectal artesunate and quality of care:** MPAG noted with concern the finding that RAS can be potentially harmful if not implemented according to WHO guidelines, i.e., RAS administration followed by immediate referral and completion of comprehensive treatment with injectable artesunate and a three-day artemisinin-based combination therapy (ACT). Based on these findings, MPAG urged the Global Malaria Programme to respond swiftly:
  - to advise countries that have not yet introduced the intervention to await further guidance before adopting and deploying RAS;
  - to notify countries that have adopted RAS about the risk of negative effects if the recommendation cannot be fully implemented, including the referral for complete treatment and ensuring the quality of care throughout; and
  - to conduct an evidence review and develop guidance for the conditions under which this tool can be implemented safely and effectively.
- **Relationship between chemoprevention and drug resistance:** MPAG recognized that drug resistance presents a potential threat to chemoprevention strategies and may increase the risk of emergence and spread of drug resistance. However, the current methodology for assessing resistance through therapeutic efficacy studies or molecular markers does not accurately reflect the impact of resistance on chemoprevention efficacy. MPAG requested that the Global Malaria Programme establish a WHO protocol for the assessment of the in vivo efficacy of antimalarial medicines when used for chemoprevention. This should be complemented by a research agenda to assess the impact of resistance on chemoprevention.
- **WHO guidelines for malaria:** MPAG commended the significant progress made using a transparent, evidence-based process following the strict guideline reviews. The value of combinations of interventions should also be explored, and where possible, appropriate recommendations developed on how countries can select and deploy combinations of interventions to increase impact.

- **Malaria vaccine:** Based on the full evidence review, MPAG and SAGE recommended that the RTS,S/AS01 malaria vaccine be used for the prevention of *Plasmodium falciparum* malaria in children living in regions of moderate to high transmission, as defined by WHO. A four-dose schedule of the RTS,S/AS01 malaria vaccine should be provided to children from 5 months of age to reduce malaria disease and burden. RTS,S/AS01 introduction should be considered in the context of comprehensive national malaria control plans.

## BACKGROUND

The World Health Organization (WHO) Global Malaria Programme convened the Malaria Policy Advisory Group (MPAG) for its 20<sup>th</sup> meeting via a virtual platform on 4–7 October 2021. MPAG generally convenes twice annually to provide independent strategic advice to WHO on technical issues related to malaria control and elimination. Over the course of the four-day meeting, 17 MPAG members, national malaria programme (NMP) managers, the WHO Secretariat, and over 400 active observers discussed updates and progress in the work areas presented. The Group discussed conclusions and recommendations to the Global Malaria Programme in a closed session on day 4.

The meeting participants were reminded of the procedures governing WHO’s assessment of MPAG members’ Declarations of Interest. All 17 MPAG members participating in the meeting updated their Declarations of Interest in advance of the meeting. These were assessed by the WHO Secretariat. Thirteen members reported interests, which are summarized and posted on the meeting website.<sup>1</sup> Five MPAG members reported relevant interests and three (Evelyn Ansah, Abdoulaye Djimde and Azra Ghani) recused themselves from the discussion and decision-making regarding the malaria vaccine. It was assessed that the remaining members could fully participate in all sessions. The stated conflicts of interest were made available for public notice and comment one week prior to the meeting. No comments were received.

## UPDATES FROM THE GLOBAL MALARIA PROGRAMME

The Director’s report reflected on the Department’s updates since April, including the updated global technical strategy for malaria (2) and the associated World Health Assembly resolution (WHA74.9) (3), the certification of China as malaria-free, intense work on guideline development and country support.

The open consultation to support the update of the global technical strategy (2) led to the update of the guiding principles, including the prioritization of country ownership and leadership with involvement and participation of communities, and the importance of a resilient health system was highlighted. The update was adopted by the World Health Assembly through a resolution (3) sponsored by the United States of America and Zambia, and co-sponsored by Botswana, Canada, Chile, China, Colombia, Eswatini, Guyana, Indonesia, Kenya, Monaco, Mozambique, Namibia, Peru, Philippines, Sudan, Switzerland and the United Kingdom of Great Britain and Northern Ireland, as well as the European Union. The resolution urges Member States to step up the pace of progress, calling on countries to extend investment in and support of health services, ensuring no one is left behind; sustain and scale up sufficient funding; and boost investment in the research and development of new tools. The Director called out the need to rethink the global malaria

<sup>1</sup> <https://www.who.int/news-room/events/detail/2021/10/04/default-calendar/20th-meeting-of-the-malaria-policy-advisory-group>

venture, as we are unlikely to progress if we continue to do the same thing. A new, problem-solving mindset is needed, driven by data, flexibility, the acknowledgement of contextual factors and the effort to overcome silos.

In June 2021, China was certified as malaria-free. Official requests for certification have been received from Azerbaijan and Tajikistan. Requests are expected soon from Belize and the Islamic Republic of Iran. The Elimination 2025 Initiative was launched with 25 countries aiming to achieve elimination by the 2025 milestone. Eight new countries were added: the Democratic People's Republic of Korea, the Dominican Republic, Guatemala, Honduras, Panama, Sao Tome and Principe, Thailand and Vanuatu. The Malaria Elimination Oversight Committee met to analyse the results of self-audits by eight national elimination programmes (the Dominican Republic, Ecuador, Eswatini, Mexico, Sao Tome and Principe, Thailand, Timor-Leste and Vanuatu) to identify strengths and weaknesses and share lessons learned.

The Global Malaria Programme is supporting capacity strengthening for malaria surveillance and response in select African countries, based on the innovative 1,7-malaria reactive community-based testing and response approach to reducing malaria burden in the south-eastern parts of the United Republic of Tanzania (4). The intervention involves mapping villages according to the highest percentage of confirmed malaria positive cases to trigger community-based mobile test and response with an artemisinin-based combination therapy (ACT) in the village the following week. The intervention has previously resulted in an 81% reduction in malaria parasite prevalence and will be supported in Burkina Faso, Senegal, the United Republic of Tanzania, and Zambia (4).

The Director highlighted the areas of armed conflict in Africa in 2021, specifically in Ethiopia's Tigray region, and the 40% increase in food insecurity up to the level of famine over 2020 that may worsen the impact of malaria. The "High burden to high impact" (HBHI) approach is continuing in 10 countries, which have all completed country reports on malaria-COVID-19, including best practices, challenges and lessons learned. The countries have been supported at national and subnational levels, and an external review is anticipated to be completed before the end of the year. Findings and recommendations will be discussed during the regional "Rethinking Malaria" meeting in early 2022.

Regarding the normative work of the Global Malaria Programme, the Director gave an update on the preferred product characteristics (PPC) under development and mentioned the upcoming consultation on monoclonal antibodies (mAbs) for malaria prevention in November. The aim of the consultation will be to develop a PPC according to the standard WHO process, using an expert Scientific Advisory Committee. The current pipeline and clinical development pathways will be reviewed, considering existing mAbs PPCs for other infectious diseases. The malaria toolkit app provides access to all WHO guidance on malaria,<sup>2</sup> including World malaria report and Malaria threats map data, on handheld devices without the need for Internet access. This makes it a useful tool in the field. Key guidance under development includes an update to the *Malaria surveillance, monitoring and evaluation: a reference manual* and a WHO global framework for the response to malaria in urban areas. The *World malaria report 2021* will include an expansion of the malaria in pregnancy section, a new section on the epidemiology and trends of severe malaria, and a section on the malaria response during the COVID-19 pandemic. The second edition of the *Guidance framework for testing genetically modified mosquitoes* (5) was published, providing essential standards to inform future research and development. A consultation on economics and insecticide resistance was held in September to define and implement a process to explicitly apply economic principles to the management of insecticide resistance in malaria vectors. An upcoming convening will update the WHO classification of glucose-6-phosphate dehydrogenase deficiency based on a nearly finished literature review.

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2 <https://www.who.int/teams/global-malaria-programme/malaria-toolkit-app>

Looking to future needs, the Director illustrated the complicated progression from inoculation with malaria to death, highlighting the various prevention and treatment interventions, co-factors that influence progression, and the importance of the various contexts within which malaria programmes operate. There is a need for flexibility in global guidance to enable appropriate packages of interventions to be applied at local levels. A new manual on the subnational tailoring of malaria interventions is in development to support this approach. This manual builds on the HBHI experience, consolidates approaches to data for decision-making to support national malaria strategic plans, and highlights the role of modelling in informing decisions on intervention mixes and prioritization subnationally.

## SUMMARY OF THE MPAG SESSIONS

### Update on “Rethinking Malaria”

**Background:** In Despite worldwide efforts and much progress in malaria control, declines in malaria morbidity and mortality have stalled. The “Rethinking Malaria in the Context of COVID-19” global engagement was constituted as a consultative process to take stock and push beyond conventional thinking. The aim is to question fundamental assumptions and approaches and focus on bold new ideas to achieve real-world progress. The process is managed by three governance bodies: a steering committee, working group co-chairs and contributing authors, and an external advisory committee.

Three public webinars were organized in June and September to enable consultation with a wider audience. Seven papers have been put together for a peer-reviewed publication on malaria governance, integrated service delivery for malaria, and training and capacity-building for malaria. These papers were shared with members of MPAG for guidance.

**MPAG conclusions:** MPAG members congratulated the group on the insightful and timely work of the “Re-thinking Malaria” initiative. MPAG members were highly supportive of the conclusions so far and highlighted the importance of making this a “whole of government and whole of society” approach. MPAG noted that, while there are many technical challenges that require serious consideration, the re-conceptualization should recognize malaria as a social and political problem, not just a disease issue. Members noted the emphasis on the critical need to focus on malaria as a symptom of inequity, which, in the view of the authors, should be addressed through whole system and multisectoral approaches. Members further suggested expanding such multisectoral approaches to include new networks for malaria, such as water, sanitation and hygiene (WASH) and antimicrobial resistance (AMR) groups.

MPAG noted that the proposed capacity-building should address broader human resource issues, such as the availability of jobs for the workforce being trained. Members expressed interest in applying the lessons learned from integrated service delivery by multisectoral partners in contexts involving migrants, emergencies, refugee populations and armed struggle, as highlighted in the Director’s report.

MPAG suggested that the rethinking Malaria process should include an in-depth critical analysis of the current situation at the national and even subnational level to identify specific elements to be changed in each context. Mechanisms should also be established to ensure timely interventions for course correction. This could be discussed at planned stakeholder meetings and carried out in collaboration with local academic institutions. The importance of strengthening effective partnerships between academics and

implementers was also emphasized. MPAG reinforced the need to adopt more innovative malaria control and elimination approaches; maintain a problem-solving mindset; increase the engagement of civil society organizations and front-line health workers; and support local manufacturers.

MPAG recommended that in moving the ideas of the papers forward, the WHO Regional Office for Africa should ensure that some critical issues raised in the papers are not overlooked in the response. An action plan needs to be drafted, ensuring that malaria is part of universal health coverage and enhancing the mobilization of domestic resources. Within the action framework, there is the need to: i) develop a framework of activities, ii) hold regular stakeholder meetings, iii) expand HBHI implementation, and iv) enhance the capacity of the Regional Offices for Africa and the Eastern Mediterranean to drive change.

## Technical consultation on non-inferiority evaluations of vector control tools

**Background:** In WHO vector control evaluation process transitioned from the WHO Pesticide Evaluation Scheme to the Prequalification Team for Vector Control in 2017. The evaluation process has continued to evolve, with the latest guidance having been published in late 2020 in the form of a document entitled *Norms, standards and processes underpinning development of a WHO recommendation on vector control (6)*. The guidance outlines the two parallel pathways. One is designed to assess new (“first-in class” [FIC]) interventions and guide the generation of epidemiological impact evidence to enable such assessment. The other pathway is designed to confirm the safety, quality and entomological efficacy of all vector control products, irrespective of whether they are first or second in class (SIC), with the aim of supporting WHO prequalification and an associated listing.

SIC interventions are not required to demonstrate epidemiological impact. Therefore, it remains unclear whether their impact in the field against the target disease(s) is at least equivalent to that of the FIC product that established the intervention class. MPAG requested WHO to investigate whether assessments of non-inferiority of SIC products based on entomological end-points could provide some form of reassurance that impact under field conditions is likely to be as good as that of the product for which epidemiological impact data are available.

In late 2018, WHO published a notice of intent on the potential introduction of non-inferiority assessment as part of the vector control evaluation process and posted a draft protocol for public consultation. This study protocol was designed to generate data to inform an assessment of the potential value of non-inferiority trials as part of the vector control evaluation process. Based on public feedback, the study protocol was finalized in early 2019 and trials on pyrethroid-piperonyl butoxide (PBO) nets were conducted thereafter to provide a case study.

The goal of the technical consultation was to evaluate the data generated in these two trials and to formulate a recommendation to WHO on the next steps regarding the use of non-inferiority assessments in the vector control evaluation process. The meeting objectives were:

- to determine whether there is value in the use of non-inferiority assessments based on the datasets generated for pyrethroid-PBO nets;
- to identify the advantages, disadvantages and potential challenges associated with the use of a non-inferiority study design and with the interpretation of data generated by such studies;

- where appropriate, to make specific suggestions on how the identified challenges could be addressed and on improvements to the current protocol/ methods, as well as on research gaps; and
- to suggest ways in which non-inferiority data could be made public if the method were to be adopted as standard practice.

The summary recommendations, as presented during the public meeting, were as follows:

- Non-inferiority studies have value in determining whether SIC products should be covered by a WHO recommendation formulated for a FIC product. The approach should be adopted as a general procedure across vector control interventions, not limited to pyrethroid-PBO nets.
- Vector mortality is to be used as the primary end-point for pyrethroid-PBO nets and for other products whose primary entomological mode of action is the killing of mosquitoes.
- Blood-feeding can be included as a secondary end-point to assist in informing programmatic and procurement decisions, but there is no requirement for non-inferiority analysis.
- For intervention classes with other entomological modes of action, other end-points should be used to inform a non-inferiority assessment.
- For insecticide-treated nets (ITNs), unwashed and 20-times washed nets should be tested. The results of both should be reported, with the primary non-inferiority analysis (vector mortality) performed on the combined results.
- The primary end-point should be calculated based on data for the dominant vector species (or species complex) only.
- A minimum of two independent trials are needed, ideally from different geographical regions. Data from each trial should be analysed separately.
- Non-inferiority needs to be demonstrated in at least two trials. If results from one of the two trials are inconclusive or one trial shows inferiority, a third trial is required.

The consultation also highlighted key research gaps regarding the measurement of end-points and durability.

**MPAG conclusions:** MPAG commended WHO for the cross-departmental work on this important issue and adopted the proposed approach for the non-inferiority evaluation of vector control tools, as well as the other detailed recommendations made in the meeting report.

Key discussion points and areas of clarification centred on seven broad topics:

- 1) clarification that manufacturers would be expected to run the non-inferiority trials as part of generating a data package for WHO assessment of a new or existing product;
- 2) issues around SIC products and selection of the comparator, which could potentially result in the exclusion of products that may be effective but unable to demonstrate non-inferiority because of the high bar set by the FIC product, or the inclusion of products that perform poorly but would not be identified as inferior because of the wide confidence intervals of the comparator;
- 3) the exclusion of certain end-points from this type of evaluation, such as physical durability, and other factors that might impact end-user acceptance of the product;
- 4) the potential risk for non-inferiority evaluations to discourage



innovation; 5) the relationship between entomological end-points and epidemiological end-points, including how non-inferiority trials of products with other entomological modes of action should be conducted; 6) the impact of insecticide resistance in trial areas on non-inferiority evaluations; 7) the perceived lack of clarity that remains among some partners around how classes of products are determined; and 8) further work is required to define and evolve the parameters of non-inferiority studies.

## Malaria rebound

**Background:** The Global Malaria Programme has commissioned a review and is planning to convene a technical consultation on malaria rebound. Malaria rebound is generally considered to be a period of increased malaria risk after time-limited protection from malaria, for instance after chemoprevention, vaccination and/or vector control, relative to individuals of the same age who did not receive the intervention. However, various definitions of the term rebound are in use. A literature review of studies evaluating rebound will consider the definitions used, interventions, target age groups, follow-up methods and periods, and presence or absence of rebound for different outcomes. The findings will inform a standardized definition and approaches to the measurement of rebound in studies evaluating new strategies or interventions.

Previous definitions include: 1) higher susceptibility to severe malaria among the recipients of a malaria control intervention when the intervention is withdrawn, compared to contemporaneously followed individuals in the same population who did not receive the intervention (Joint Technical Expert Group on Malaria Vaccines, 2015 (7)); and 2) an increase in the incidence of malaria after a period when effective malaria control has been achieved (by any means) above the incidence that would have occurred if the intervention had not taken place.

The objectives of the technical consultation will be to review existing evaluations of the rebound phenomenon, drawing attention to differences in the definition and approach to measuring; considering the extent to which rebound could be a public health problem; agreeing on the key issues in the design of studies evaluating new strategies or interventions; and considering approaches to ameliorate the effects of rebound.

**MPAG conclusions:** Members were very supportive of the need for this review, as there are implications for individuals who may be at risk following a targeted intervention that impairs the development or maintenance of clinical immunity, and for communities at risk of epidemic malaria following a malaria-free period, for example, following chemoprevention or vector control, or when there is rainfall following several years of drought. The review will assist in the design of studies to assess the potential for rebound following the use of new strategies or interventions and help to determine the public health measures to be implemented when interventions are scaled down or ceased.

Several members commented on the need for standardized definitions for malaria rebound and consideration of “age shift”, which refers to a change in disease pattern characterized by a permanent reduction in transmission. Assessment should look at data following protection by different strategies targeting pre-erythrocytic or erythrocytic stages, and for different durations of interventions and follow-up periods, where available. Inclusion of available clinical and parasitological data would be desirable, as would assessment of the quality of health services and diagnostic capacity (“routine” or “research”) during follow-up. Studies that could potentially be included were referenced, such as the Garki Project in Nigeria and the Blue Nile project undertaken in the Gezira Province of Sudan several decades ago. Members noted the importance of understanding the disease burden in populations and level of clinical immunity prior to the intervention; seasonality; age-associated change in risk; duration of the intervention; and nature of health services in the follow-up period. There were many suggestions



about issues to be considered in assessing the quality and generalizability of the reported studies and factors that will need to be addressed if new studies are planned.

## Antimalarial drug resistance in Africa

**Background:** The presentation covered two main topics: monitoring antimalarial drug efficacy in Africa with an update on polymerase chain reaction (PCR) correction, which was the topic of an informal consultation, and the current situation with antimalarial drug efficacy and resistance in Africa.

The informal consultation was data-driven and assessed the advantages and disadvantages of changing the way recurrences are differentiated as reinfection or recrudescence following the treatment of uncomplicated *Plasmodium falciparum* malaria. This differentiation has implications for the evaluation of antimalarial efficacy in therapeutic efficacy studies (TES), as well as in regulatory trials for the development of new antimalarial drugs. The consultation examined evidence around changes in the genetic markers used to determine the relatedness of initial and recurrent parasites, as well as the algorithms used to analyse these markers to classify recurrences as either recrudescence or reinfection. In particular, the panel examined the applicability of recent advances in genotyping and analysis. The meeting focused on areas of high transmission in Africa because the high multiplicity of infection (i.e. the number of concurrent clones in an infection) and high reinfection rates in such areas complicate the discrimination of recrudescence from reinfection.

The three recommendations from the meeting were as follows:

1. As an interim solution, *msp1* and *msp2* should continue to be used, but *glurp* should be replaced with a panel of two to three carefully chosen microsatellites (such as *Poly-α*, *Pfprk2* and *TA1*), customized to provide sufficient local diversity at least at the country level, or regionally if possible. For simplicity and reasons of practical implementation, match-counting should be maintained as the primary analysis methodology for reporting. These methods should be applied in both low to moderate and high transmission settings in Africa. Bayesian algorithms may be applied for evaluation and comparison, but not for primary reporting. Outside Africa, the current method (*msp1/msp2/glurp*) should still be applied.
2. For a transition period, data should be analysed and reported using both the current (*msp1/msp2/glurp*) and new (*msp1/msp2/microsatellites*) methods to enable historical comparison and to understand the implications of the new methods in terms of thresholds for treatment policy change and introduction of new antimalarial drugs. Data transparency will be critical for comparative analysis and to provide a database for analytical methodology development.
3. As a medium-term (five-year) target, AmpSeq should be evaluated in parallel across Africa and outside Africa to compare it with current methods at sites and to validate whether this genotyping methodology should be adopted as the standard. A simple match-counting algorithm complemented by a Bayesian algorithm could be paired with this approach, but more comparative data are needed to inform a recommendation on the algorithm for analysing AmpSeq results.

The update on the situation with antimalarial drug efficacy and resistance, including resistance to artemisinin and partner medicines, covered prevention and response activities to address antimalarial drug resistance, and discussion on the development of a protocol for chemoprevention. The K13 genotypes in Africa countries from 2015 to 2020 were summarized, and five countries were identified as having more than 5% K13 mutations: Cabo Verde, Eritrea, Ghana, Rwanda, and Uganda. Therapeutic efficacy

studies (TES) have looked at the efficacy of ACTs, including artemether-lumefantrine (AL), artesunate + sulfadoxine-pyrimethamine (ASSP), artesunate-amodiaquine (ASAQ), artesunate-mefloquine (ASMQ), artesunate-pyronaridine (ASPY) and dihydroartemisinin-piperaquine (DP). These studies have identified treatment failure rates of more than 10% for AL and DP in Angola, Burkina Faso and the Democratic Republic of the Congo. A review of the data was undertaken to determine whether there is lumefantrine resistance in Africa; however, the results remain inconclusive, with signals both for and against the presence of resistance. A recent WHO publication summarizes interventions to prevent and respond to resistance (8).

The final update was on work to develop a protocol for chemoprevention efficacy surveillance (CPES). WHO currently recommends intermittent preventive treatment of malaria in pregnancy (IPTp), intermittent preventive treatment of malaria in infants (IPTi) and seasonal malaria chemoprevention (SMC), but there is no standardized approach for monitoring and evaluating the efficacy of these strategies. Molecular markers have been found to be associated with treatment outcomes, but the predictive value for the efficacy of chemoprevention is still unclear and they are unreliable for making implementation decisions. CPES studies are single-arm studies that evaluate the ability of one round of chemoprevention to prevent parasitaemia for a predefined period of follow-up. The protocol is under development and will be presented to MPAG at a future meeting.

**MPAG conclusions:** MPAG commended the detailed report from the informal consultation on the methodology to distinguish reinfection from recrudescence in high malaria transmission areas and accepted the proposed recommendations. During the discussion, it was noted that *glurp* is problematic in many places, and it was clarified that countries are not required to use *glurp* if they have already switched to other microsatellite markers.

MPAG noted the comprehensive update on artemisinin and partner drug resistance. The Group raised concerns about reports of artemisinin partial resistance in Rwanda and Uganda, and treatment failures with AL and DP in Angola, Burkina Faso and the Democratic Republic of the Congo. The Group noted the need to act quickly to respond to the threat of artemisinin partial resistance and to confirm whether resistance to key partner drugs such as lumefantrine and piperaquine has emerged.

MPAG requested that the Global Malaria Programme develop a regional response plan to address the threat of artemisinin partial resistance, highlighting that investment is urgently needed to support this response. Countries will seek guidance on what rates of resistance require a change of ACTs, and what are the preferred options for alternative combinations. Given the importance of this threat, MPAG requested the Global Malaria Programme to provide an update in the next meeting.

MPAG recommended conducting high-quality efficacy surveillance, systematically incorporating tools such as molecular markers and where possible, *ex vivo* tests to confirm the emergence of resistance to key partner drugs. In addition, the Group asked the Global Malaria Programme to explore options to tackle the potential risk of reduced efficacy of the partner drugs within the artemisinin-based combinations. Research should be encouraged to explore topics that could help to lessen the dependence on a few ACTs, including rolling out alternative ACTs, rotating ACTs or using non-artemisinin-based combinations as soon as they become available. The Global Malaria Programme should also assess the evidence to determine whether adding low-dose primaquine for transmission-blocking could be recommended more widely.

## Rectal artesunate (RAS) and quality of care

**Background:** WHO has recommended RAS as an effective pre-referral treatment for severe malaria in children under 6 years of age. The recommendation comprises three components based on the continuum of care: RAS administration, immediate referral to a facility where comprehensive severe malaria care can be provided, treatment with injectable artesunate and completion of treatment with full ACT treatment. Uptake of this recommendation has been suboptimal, partially due to the unavailability of prequalified RAS. The CARAMAL project was designed to generate evidence to support the development of operational guidance for the implementation and scale-up of RAS, since RAS has become commercially available at a WHO-prequalified standard, enabling large-scale procurement with international financing. The project relied on two components: RAS implementation in the context of established Integrated Community Case Management (iCCM) programmes; and a large operational research component. The research component of the CARAMAL project tested the hypothesis that it is feasible to achieve reductions in severe malaria case fatality ratios by delivering RAS through established iCCM platforms without unintended negative consequences. The data were reviewed at a WHO technical consultation in April with the intention of developing operational guidance.

In the evidence that led to its recommendation in 2007, RAS was shown to reduce deaths in controlled or strongly supported settings – which is unlikely to reflect real-world implementation scenarios. Evidence generated by the CARAMAL project demonstrated the many challenges along the cascade of care and showed no positive effect of pre-referral RAS on the case fatality rate in one of the settings and an increase in the other two settings, all highly malaria endemic settings in Africa. Project findings demonstrated reduced referral completion, leading to incomplete treatment and missing of other infections and comorbidities. Post-referral treatment was often incomplete and, in particular, the required three-day ACT was not consistently administered, leaving patients with RAS/injectable artesunate as artemisinin monotherapy. There was a higher case fatality rate in children using RAS, which could be due to secular or seasonal trends in the diagnosis and treatment of comorbidities and other factors. In addition, incomplete treatment may exacerbate the selection and spread of artemisinin-resistant parasites.

The project was purposely designed to introduce RAS into established community platforms with only minimal supportive interventions. Challenges with community health worker (CHW) networks were indicated by the very low percentages of febrile children reportedly taken to CHWs in the study areas. Challenges with care at referral facilities included stockouts and inadequate staffing. There were also challenges with the accuracy and completeness of data reported in routine information systems).

**MPAG conclusions:** MPAG appreciated the data presented from the RAS implementation study, which used an observational before and after plausibility study design. The study results demonstrated the difference between intervention efficacy evaluated in well-controlled study settings and intervention effectiveness under real-life conditions in trial subgroups. MPAG noted with concern the finding that RAS can be potentially harmful if not implemented according to WHO guidelines, i.e., RAS administration followed by immediate referral and completion of comprehensive treatment with injectable artesunate and a three-day ACT. MPAG further noted the risk of contributing to selection of resistance through monotherapy if the full recommended treatment is not completed.

Based on these findings, MPAG urged the Global Malaria Programme to respond swiftly:

- to advise countries that have not yet introduced the intervention to await further guidance before adopting and deploying RAS;

- to notify countries that have adopted RAS about the risk of negative effects if the WHO recommendation cannot be fully implemented, including the referral for complete treatment and ensuring the quality of care throughout; and
- to conduct an evidence review and develop guidance for the conditions under which this tool can be implemented safely and effectively.

## Relationship between chemoprevention and drug resistance

**Background:** The Global Malaria Programme has commissioned a review to look at how malaria chemoprevention strategies affect and are affected by drug-resistant malaria; how drug resistance is best measured and monitored for each chemoprevention strategy; and what approaches could mitigate the impact of resistance on chemoprevention efficacy.

The review highlighted that drug resistance is one of many potential factors determining the efficacy of chemoprevention, and clinical trials measuring health outcomes are the gold standard for measuring chemoprevention efficacy. Drug treatment efficacy is not a reliable surrogate for chemoprevention efficacy, and while molecular markers accurately indicate the presence of drug-resistant parasites, they are unable to predict chemoprevention efficacy. Specific resistance markers must be validated independently as predictors of efficacy for each chemoprevention regimen.

- IPTp with sulfadoxine-pyrimethamine (SP) appears to select for antifolate resistance mutations associated with low to moderate increases in drug resistance, but there is no convincing evidence of selection favouring the key mutations associated with a high level of antifolate resistance and loss of IPTp-SP efficacy. Despite some evidence that a high level of antifolate resistance at least partially compromises IPTp-SP efficacy, subsequent studies have not shown a worst case scenario of harmful effects in the presence of SP resistance, and the evidence supporting a recommendation to withhold IPTp-SP where the prevalence of resistance markers exceeds 10% is not strong.
- IPTi-SP has been accompanied by overall increases in the prevalence of some antifolate resistance markers. However, neither clinical trials nor ecological surveys comparing implementation zones to control areas over time have shown evidence of significant selection of the resistance haplotypes associated with SP efficacy for treatment or chemoprevention. The recommendation that IPTi-SP should not be deployed where the prevalence of resistance markers exceeds 50% was based on evidence from two trials 10 years ago. Little new evidence is available to validate this threshold or set new criteria to guide IPTi policy. Prevention efficacy studies remain the gold standard to guide policy.
- While some studies have reported that SMC is followed by increased prevalence of resistance markers, other studies have found no evidence of selection. There is no evidence that SMC results in increased prevalence of the higher-level resistance mutations that most severely impair SP efficacy, nor does SMC appear to select for parasites carrying mutations associated with amodiaquine resistance. Until high-level resistance mutations become more prevalent in areas where SMC is used, it will not be possible to draw conclusions about the impact of resistance on SMC efficacy.
- In the Greater Mekong subregion, a cluster-randomized trial of mass drug administration (MDA) with dihydroartemisinin-piperavaquine (DP) in sites with varying levels of resistance found very few post-MDA infections and no evidence

of selection for resistance markers. In Mozambique, prevalence of resistance markers was compared before and after MDA with DP and no evidence of selection for resistance markers was found. There is no evidence that MDA in the modern era using highly effective ACTs results in increased drug resistance. In the past, drug resistance diminished the efficacy of MDA when drugs were used in sub-curative formulations and dosing regimens. However, in the 21<sup>st</sup> century, MDA with highly effective combination drugs has proven efficacious, even in the face of high levels of resistance.

Standardized protocols for measuring and monitoring chemoprevention efficacy are needed. With imperfect evidence, practical considerations can help guide recommendations on when and where to deploy chemoprevention strategies. Using different drugs for chemoprevention and treatment and combining drugs with countervailing resistance mechanisms may help to preserve efficacy. The best approach for mitigating and managing drug resistance to protect the efficacy of chemoprevention strategies is to ensure a pipeline of safe and effective new malaria drugs with diverse mechanisms of action and resistance.

**MPAG conclusions:** MPAG thanked the presenter for his comprehensive and critical review of the literature. MPAG recognized that drug resistance presents a potential threat to chemoprevention strategies. However, the current methodology of assessing resistance through therapeutic efficacy studies (TES) or molecular markers does not accurately reflect the impact of resistance on chemoprevention efficacy. Therefore, MPAG requested that the Global Malaria Programme establish a WHO protocol for the assessment of the in vivo efficacy of antimalarial medicines when used for chemoprevention. This should be complemented by a research agenda to assess the impact of resistance on chemoprevention.

MPAG also recognized the urgent need for the development of new drugs for chemoprevention. The Global Malaria Programme and Medicines for Malaria Venture are developing a preferred product characteristics (PPC) for chemoprevention, and MPAG emphasized the need to move this agenda forward as quickly as possible. MPAG also encouraged consideration of including drugs with gametocytocidal activity in chemoprevention strategies.

MPAG noted the complexity of the emergence and progression of drug resistance in the chemoprevention space. The relative fitness of mutant parasites in the presence and absence of the drug, the role of immunity (particularly in IPTp, IPTi and MDA settings), the impact of transmission intensity, the quality of drugs, subject compliance, pharmacokinetics, and the mechanism of action of chemoprevention drugs are all likely to impact the efficacy of a chemoprevention strategy. MPAG suggested that longitudinal studies and modelling studies could provide useful insights for guiding decisions on a change in chemoprevention drugs. These aspects, along with the economic implications of failures, adverse drug reactions and changes to alternative drugs, should be considered when developing recommendations.

## **Update on the WHO guidelines for malaria**

**Background:** Severe The pathway for developing guidelines in the Global Malaria Programme is articulated in three phases: 1) better anticipate, 2) develop recommendations, and 3) optimize uptake with a feedback loop to enable continuous updates and improvement. The *WHO guidelines for malaria (1)* were first published in February 2021, consolidating all of the recommendations across the different areas of prevention and case management. The French translation has been published, and the Spanish and Arabic translations are ongoing. The Guidelines are available through

the MAGICapp online platform,<sup>3</sup> via a PDF on the Global Malaria Programme website, and through the malaria toolkit app for mobile devices.<sup>1</sup> Work is ongoing to develop living reviews to inform living guidelines to rapidly update recommendations for which new evidence becomes available; a dissemination strategy to improve how the recommendations are packaged and shared to optimize uptake by end-users; and a manual to support the subnational tailoring of malaria interventions.

There are currently four Guideline Development Groups (GDGs) convened to support the review of evidence and formulation of recommendations on vector control, elimination, chemoprevention and treatment. A joint process is underway to assess the evidence related to the malaria vaccine, and a proposal to convene a GDG for diagnosis is under development. The technical focal points shared the areas of work for which evidence reviews are underway and the timelines for publishing updated and new recommendations. The first update was published in July 2021 and included the following updates for vector control: expanded background information on how nets work, edited information on insecticide resistance monitoring and interpretation, a new recommendation on house screening, and an evidence review of larval habitat manipulation and modification that did not result in a recommendation.

Challenges that the team is managing include lack of sufficient data on the impact against malaria, variable certainty of evidence, and determination of when “no recommendation” can be made. In addition, multiple interventions being applied at the same time can make it difficult to assess the impact of a particular intervention under review. The importance of shaping the research space when more evidence is needed was recognized, so that a recommendation is not a disincentive for further innovation. Consistency in wording across the groups is a priority, as is the balance between being prescriptive, so that countries have the information they need to plan implementation, and being flexible, so that mixes of interventions can be tailored to the local context.

**MPAG conclusions:** MPAG commended the significant progress made using a transparent, evidence-based process following the strict guideline reviews. In particular, members noted the new and updated recommendations from the past year, and the clarity of the guideline development process. The Group suggested that more detail on monitoring and evaluation be added to the recommendations, particularly guidance on selecting indicators for the main interventions.

MPAG noted the ongoing efforts to improve the consistency of the wording of the recommendations across the technical areas. MPAG commented on the importance of considering field data and feedback from implementation in the formulation of recommendations, in addition to randomized trials. The value of combinations of interventions should also be explored and, where possible, appropriate recommendations developed on how countries can select and deploy combinations of interventions to increase impact. Evaluation of control tools should be context-specific and could be conducted by the countries to guide their own strategies.

MPAG suggested that there is a need to clarify that WHO may choose to make no recommendation when there is a lack of sufficient evidence to support an intervention’s deployment. This is distinct from there being evidence that an intervention is ineffective, in which case, WHO would make a recommendation against deployment. The Group noted that the development of recommendations should be linked to the “Rethinking Malaria” initiative. Because WHO guidelines should be operationalized at the field level through country support, MPAG supported the engagement of end-users, including field

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<sup>3</sup> <https://app.magicapp.org/#/guideline/5438>

workers and stakeholders, as external reviewers to help facilitate operationalization of the guidelines.

## Joint Strategic Advisory Group of Experts on Immunization (SAGE)/MPAG session on the malaria vaccine

**Background:** May In a joint session, MPAG and SAGE were presented with evidence on the feasibility, impact and safety of the RTS,S/AS01 malaria vaccine and were requested to advise on the broader use of the vaccine in children beyond the current pilot implementation.

Malaria remains a primary cause of childhood morbidity and mortality in sub-Saharan Africa, with more than 260 000 child deaths from malaria annually. After considerable gains in the past two decades, progress with malaria control has stalled, and renewed efforts and new tools are urgently needed. The results of the Phase 3 clinical trial and the considerations that led to the WHO recommendation in 2016 for pilot implementation of the RTS,S/AS01 vaccine were reviewed. The Malaria Vaccine Implementation Programme (MVIP) was established by WHO on advice from MPAG and SAGE to coordinate and support national immunization programmes in Ghana, Kenya and Malawi to introduce the RTS,S/AS01 vaccine in selected areas and to conduct a rigorous evaluation of the programmatic feasibility of administering four doses; the safety of the vaccine in routine use, with particular attention to the safety signals observed in the Phase 3 trial (meningitis, cerebral malaria, and excess mortality in girls); and vaccine impact in routine use.

The MVIP Data Safety and Monitoring Board (DSMB) found no evidence of the safety signals seen in the Phase 3 trial in the pilot evaluations. The vaccine has an acceptable safety profile, and no new safety signals were identified through the MVIP or routine pharmacovigilance. The African Advisory Group on Vaccine Safety (AACVS) and the Global Advisory Committee on Vaccine Safety (GACVS) reviewed the safety data and concurred with the DSMB assessment. Given the rigour and size of the pilots, GACVS and AACVS do not recommend that vaccine-specific safety monitoring be put in place before broader use. The manufacturer-sponsored Phase 4 post-authorization study continues until 2025 as part of the risk management plan with the European Medicines Agency (EMA). Since July 2015, the EMA has maintained a positive scientific opinion on the vaccine under Article 58.

The findings from the pilot evaluation demonstrate a statistically significant 30% reduction in hospitalized severe malaria and a 21% reduction in hospitalization with malaria parasitaemia following delivery of the vaccine through routine immunization programmes, in the context of existing malaria control measures. Modelling studies estimate a significant public health impact, with an estimated cost per disability-adjusted life-year (DALY) averted of US\$ 97–103 (assuming a vaccine price of US\$ 5/dose) in settings with moderate to high malaria transmission. The pilot programme found no impact on the uptake of routine vaccinations, health care-seeking behaviours or ITN use. Surveys indicate equitable coverage and the potential to increase access to malaria prevention by layering interventions.

A three-year study conducted in settings of highly seasonal malaria where SMC is implemented has yielded new evidence that providing three doses of RTS,S (at monthly intervals before the peak transmission season, with annual doses thereafter) is non-inferior to administering four rounds of SMC. The combination of the two interventions resulted in a substantially lower incidence of uncomplicated or severe malaria and malaria-specific mortality than either intervention alone.



**MPAG and SAGE conclusions:** MPAG noted that the importance of ITNs to the control and elimination of malaria, coupled advisory groups acknowledged the adequacy of information now available to address the questions they raised in 2015. Data from the MVIP have demonstrated that the vaccine can be delivered successfully. The vaccine has been incorporated into the national immunization programmes by the ministries of health in the three participating countries using the usual process for new vaccine introduction. Vaccine uptake reached or exceeded expectations for a new vaccine with a novel schedule, even in the context of the COVID-19 pandemic. Since April 2019, over 2.3 million vaccine doses have been administered and over 800 000 children have been reached with at least one dose.

Based on the full evidence review, MPAG and SAGE recommended that RTS,S/AS01 malaria vaccine be used, alongside other WHO recommended malaria control measures, for the prevention of *P. falciparum* malaria in children living in regions with moderate to high transmission, as defined by WHO. A four-dose schedule of the RTS,S/AS01 malaria vaccine should be provided to children from 5 months of age to reduce malaria disease and burden.

Drawing from a growing body of evidence, countries may consider providing the RTS,S/AS01 vaccine seasonally, with a five-dose strategy (i.e. a primary course of three monthly doses, followed by two annual seasonal doses) in areas with highly seasonal malaria or in areas with perennial malaria transmission with seasonal peaks. When countries choose the seasonal deployment of the RTS,S/AS01 vaccine, they are strongly encouraged to document their experience, including the vaccine's effectiveness and feasibility, and occurrence of any adverse events, in order to inform future guidance updates. In addition, WHO encourages funders to support a relevant learning agenda. Seasonal deployment of the RTS,S/AS01 vaccine constitutes an off-label use of the vaccine.

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All documentation related to this meeting can be found at:  
<https://www.who.int/news-room/events/detail/2021/10/04/default-calendar/20th-meeting-of-the-malaria-policy-advisory-group>

All previous MPAG meeting reports can be found here:  
<https://www.who.int/groups/malaria-policy-advisory-group/meeting-archives>

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