

WHO Malaria Policy Advisory Group (MPAG) meeting

APRIL 2021

MEETING REPORT

SUMMARY

On 13–15 April 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 (GMP).

The virtual meeting focused on nine topics in four open sessions: 1) “Rethinking Malaria”; 2) clinical malaria: parasite density analysis and implications for diagnostic test specifications; 3) an update on the situation of antimalarial drug efficacy and resistance in Africa; 4) a proposed technical consultation to stage *P. knowlesi* along the continuum between zoonosis and human pathogen; 5) an update on the threat of *pfhrp2/3* deletions in the Horn of Africa; 6) a proposed technical consultation on the response to malaria in urban areas; 7) an update on guidance for severe malaria; 8) an update on work related to implementing a revised classification of insecticide treated net (ITN) products; and 9) an update on Digital Solutions for Malaria Elimination (DSME) surveillance).

The key conclusions of MPAG to GMP included:

- **Rethinking Malaria:** MPAG supported the “Rethinking Malaria” agenda and process. While the agenda acknowledges health system deficiencies, MPAG felt that it needs further thought to fully engage with the complexities and the structural inequities that underpin actions and responses to malaria.
- **Clinical malaria: parasite density and implications for diagnostic tests:** MPAG was reassured with the analysis supporting the view that the minimum sensitivity requirements of currently available rapid diagnostic tests (RDTs) and microscopy are sufficient to capture the vast majority of clinical malaria cases in sub-Saharan Africa. MPAG emphasized that other causes of fever should always be actively investigated, even if the RDT is positive. MPAG encouraged implementation research

to determine the clinical and public health impact of identifying and treating patients attending health facilities with *P. falciparum* parasite densities below the identified threshold. MPAG recommended that a similar analysis be undertaken outside sub-Saharan Africa for *P. falciparum* and *P. vivax*.

- **Antimalarial drug efficacy and resistance in Africa:** MPAG members appreciated the presentation and agreed with the conclusions on the need for continued surveillance outside the GMS to change first-line treatment when failures reach a critical level, to validate mutants and to monitor worldwide artemisinin resistance. MPAG strongly recommended the proposed activities to minimize the risk of emergence and spread of resistance. MPAG further recommended that efficacy and resistance studies should use standard methodology to ensure comparability and high-quality results, and highlighted the need to validate mutations with clinical response.
- **Technical consultation to stage *P. knowlesi*:** MPAG supported the proposed technical consultation and noted that the key question is whether there are sustained chains of *P. knowlesi* transmission events that do not involve primates, and whether this requires reclassification of *P. knowlesi* as a human malaria parasite. MPAG recognized that the results of the technical consultation could have significant ramifications for the malaria community and public communication on the implications for certification of elimination should be considered independent of the staging of *P. knowlesi*. MPAG suggested that the systematic review team ensure that genomic data are reviewed and requested that the technical consultation consider the need and feasibility of conducting more in-depth prospective epidemiological and genomic investigations to find clear evidence for or against sustained human–vector–human transmission.
- **Threat of *pfhrp2/3* gene deletions in the Horn of Africa:** MPAG noted that the issue of HRP2 gene deletions has emerged as a threat that requires urgent attention, as it has the potential to derail the gains made in reducing malaria mortality. MPAG further noted that innovative ways must be found to provide the needed resources to adequately map this urgent problem. MPAG emphasized the need for research and development of improved non-HRP2-based RDTs and the need for research on the drivers of emergence and selection for *pfhrp2/3*-deleted parasites to guide efforts to combat their expansion. MPAG noted with concern the reluctance of some countries to switch to non-HRP2-based RDTs, despite undisputedly high prevalence of *pfhrp2* gene deletions that surpasses the WHO-recommended criterion for change. MPAG called for affected countries to take urgent action and resolved to issue a statement to encourage such action.
- **Technical consultation on urban malaria:** MPAG congratulated WHO for the initiative to convene a technical consultation on the burden and response to malaria in urban areas and agreed that this was a timely activity. MPAG noted that it will be important to recognize the heterogeneity in access to health services within urban spaces, to understand accessibility and potential effects on drivers and patterns of disease. MPAG supported the need to differentiate between the place of infection and place of diagnosis to define effective control strategies. The Group emphasized the importance of making micro-stratification approaches, integrated vector management (IVM), continuous monitoring, and a multisectoral approach central topics of discussion in the consultation.
- **Severe malaria:** MPAG endorsed the proposed plan to update the *Management of severe malaria: a practical handbook* and to develop operational guidance for the use of rectal artesunate, with an emphasis on the importance of follow-up combination therapy and noted the need for enhanced country support and

human capacity development for successful outcomes. MPAG supported the plans for implementation and country support to update national policies and build the required systems and capacity to effectively manage severe febrile illness, including severe malaria.

- **Classification of ITN products:** MPAG recognized the significant progress that has been achieved on classification and evaluation of ITNs as a means to expedite a WHO recommendation and prequalification and appreciated annual updates. MPAG felt that while the present ITN classification system of three classes based on entomological effect is not perfect, it does provide a clear and needed framework for defining a first-in-class product requiring evidence of epidemiological effectiveness in two trials and the need for non-inferiority data for second in class products. MPAG strongly supported the continued investigation on the use of non-inferiority study designs to generate data to compare product performance within a class, as well as the planned technical convening in September 2021.
- **DSME surveillance:** MPAG congratulated WHO on this initiative and felt that it demonstrates a significant improvement with fit-for-purpose tools that programmes can use to support implementation of elimination activities. MPAG recommended that as part of the dissemination plan, it would be useful to provide clear information for national malaria programmes (NMPs) to consider before undertaking the digital transition to these tools, including clarifying the settings in which these tools are applicable.
- **High-level recommendation:** MPAG emphasized the need for WHO to consider its approach to capacity building and the implementation of guidance across the range of technical areas for malaria in the context of a need for broader health systems strengthening. MPAG strongly supports the need to strengthen the collection and use of data to move beyond the one-size-fits-all approach. The use of subnational data will inform stratified implementation plans that can be tailored to local contexts to maximize impact, and lessons learned from the success of other countries can be shared. MPAG requested an agenda item dedicated to capacity building at the next MPAG meeting.

BACKGROUND

The World Health Organization (WHO) Global Malaria Programme (GMP) convened the Malaria Policy Advisory Group (MPAG) for its 19th meeting via a virtual platform on 13–14 April 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 two-day meeting, 17 MPAG members, national malaria programme (NMP) managers, the WHO Secretariat, and over 200 active observers (of 473 registered) discussed updates and progress in the work areas presented. The Group discussed conclusions and recommendations to GMP in a closed session on day three.

The meeting participants were reminded of the procedures governing WHO's assessment of MPAG members' declarations of interest. All 17 MPAG members attending the meeting submitted their declarations of interest, which were assessed by the WHO Secretariat. Twelve members reported conflicts of interest, but none were relevant to the topics for decision on the agenda. A due diligence search was undertaken and found nothing significant that had not already been declared by the MPAG members.

UPDATES FROM THE GLOBAL MALARIA PROGRAMME

The GMP Director began his report by reflecting on the 20 years of progress and challenges summarized in the *World malaria report 2020*. There was a 29% reduction in global malaria case incidence between 2000 and 2019, but less than a 2% reduction between 2015 and 2019. In the same period (2000–2019), there was a 60% reduction in global malaria mortality incidence, with about a 15% reduction between 2015 and 2019. At the same time, between 2000 and 2019, the population in sub-Saharan Africa (where 94% of global malaria cases and deaths occurred in 2019) grew from 665 million to about 1.1 billion. The Director described the recent history of malaria in five periods: the 1990s, which set the foundation; 2000 to 2015, which was the era of scaling up and making an impact toward the Millennium Development Goals; 2015 to 2019, which saw a plateauing of funding and progress; 2020, which was the year of COVID-19; and now – a time for rethinking, learning and adapting. He finished outlining the current context by showing the trajectory of progress that will be needed to achieve the 2030 goals of the *Global technical strategy for malaria 2016–2030* (GTS) and the forecasted trend if the current trajectory is maintained.

The Director provided updates on current areas of work, including the update of the GTS, which will be reviewed by the seventy-fourth World Health Assembly in May and published soon thereafter, and updates on the department's normative work to better anticipate, develop recommendations and optimize impact. In the area of "better anticipate", the work on the development of preferred product characteristics (PPCs) for vector control tools, malaria vaccines and chemoprevention drugs was presented, and an update on the progress of the Malaria Vaccine Implementation Project (MVIP) indicated that a full evidence review will be done by the Programme Advisory Group at the end of May, with a joint meeting of the Strategic Advisory Group of Experts on Immunization and MPAG to consider a recommendation in October. WHO's support, together with other partners, for three additional implementation projects was discussed: 1) Community Administration of Rectal Artesunate for Severe Malaria (CARAMAL), funded by Unitaid; 2) Transforming Intermittent Preventive Treatment for Optimal Pregnancy (TIPTOP), funded by Unitaid; and 3) exploring new approaches to acceleration through surveillance and response, funded by the UN Peace Fund Agenda 2030. In the area of "develop recommendations", five guideline development groups are convened to provide new and updated recommendations this year on vector control, chemoprevention, elimination, treatment and diagnostics. In addition, the *Norms, standards and processes underpinning WHO vector control recommendations* was published to outline the evaluation process for assessing novel vector control interventions. This document replaces guidance on the vector control evaluation process issued in 2017. To optimize uptake, the consolidated *WHO Guidelines for malaria* were launched in February 2021 on the MAGICapp platform to facilitate rapid updates, with translations into French, Spanish and Arabic underway. Further work will focus on updating the mobile app content and developing short training videos to support a problem-solving approach and enable national decision-making on the optimal mix of interventions.

The department is continuing to support countries to achieve impact with the focus on the "High burden to high impact" (HBHI) approach and the Elimination 2025 Initiative. Key areas of HBHI support include: strengthening surveillance and monitoring and evaluation (M&E), retrospectively assessing possible causes of increased malaria burden and factors undermining intervention effectiveness, reviewing the proposed mix of vector control interventions, analysing quality of services, optimizing community health worker effectiveness, supporting private sector engagement, and developing subnational operational plans. The HBHI approach will also be promoted in high-burden countries beyond the original 11 through webinars, annual fora and country-specific dialogues. World Malaria Day 2021 will focus on "Zeroing in on malaria elimination" and the launch of Elimination 2025. WHO has identified a new cohort of 25 countries with the potential to eliminate malaria by 2025, with eight new countries added to the remaining E-2020 countries: Dominican Republic, Democratic People's Republic of Korea, Guatemala,

Honduras, Panama, Sao Tome and Principe, Thailand and Vanuatu. *Preparing for certification of malaria elimination* was published to provide guidance to countries approaching elimination, building on the guidance provided in the 2017 *Framework for elimination*. On 25 February 2021, El Salvador became the first country in Central America to be certified malaria-free by WHO. A request for certification was received from China and an independent evaluation mission is tentatively planned for May 2021.

PARTNER PERSPECTIVE – U.S. PRESIDENT’S MALARIA INITIATIVE (PMI)

The recently appointed U.S Global Malaria Coordinator who leads PMI joined the meeting to talk about some of PMI’s experiences as an example of what the global malaria community has accomplished, to highlight that several organizations are currently updating their strategic plans, to share early thoughts on PMI’s strategic thinking for feedback, and to recognize the opportunity to define global achievements in the coming decade against malaria. The Coordinator emphasized the achievements since the start of PMI (2006), PMI, partners, and the wider malaria community have contributed to a 29% reduction in case incidence and a 60% decrease in mortality rates in PMI partner countries. Further, PMI has contributed alongside the malaria community to saving an estimated 7.6 million lives and preventing 1.5 billion cases, with the PMI support to 27 country programmes totalling US\$ 746 million in 2020 alone. PMI has supported countries to take proven interventions to scale including the implementation of ITNs, indoor residual spraying (IRS), case management, intermittent preventive treatment for pregnant women (IPTp), and seasonal malaria chemoprevention (SMC), and made cross-cutting investments in supply chain and health systems strengthening; social and behaviour change; surveillance, monitoring and evaluation; and operational research. However, the *World malaria report 2020* continues to call out a stalling of progress. In this context, multiple organizations are undertaking strategy updates, including the RBM Partnership to End Malaria, the Bill & Melinda Gates Foundation, the United Kingdom Foreign Commonwealth & Development Office, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and WHO.

PMI is updating its strategy for 2021–2025, and the Coordinator presented a few highlights of some updated draft priorities that are under discussion. He presented a schema of how PMI thinks about these priorities within the context of the mission, the vision, and the five year strategic priorities that inform annual operational plans and budgets. The priorities are the core ideas and actions that PMI plans to focus on to shape the strategy, plans and budgets. Importantly, PMI acknowledges that “what got us here, won’t get us there”, and the Coordinator called out four draft priorities for the malaria community in order to end malaria faster:

1. Reach the unreached: we must decrease malaria deaths and disease by bringing proven interventions within reach of the last mile (i.e., remote and rural) communities – those with the highest malaria transmission and the lowest intervention coverage.
2. Make community health systems stronger: we must transform the quality of community health systems (i.e., clinic-to-community) by strengthening data, laboratories, supply chains, supervision and management systems in order to improve malaria outcomes.
3. Keep malaria services safe and resilient: we must prevent the reversal of gains by keeping malaria services safe, resilient, and effective in the face of new threats – e.g., from COVID-19, other emerging threats, resistant mosquitoes and parasites, climate change, and conflict – while contributing to global health security.

4. Invest in people and partners closest to those we serve: we must increase the sustainability of our programmes by transforming how we invest effectively in local leaders, organizations (i.e., private, non-governmental organizations, and public) and other partners.

These priorities and the work of PMI over the past 15 years were mapped to how the organization contributes to and aligns with the pillars and supporting elements of the WHO GTS. PMI is continuing to refine its strategy and welcomes feedback to: mvenkatesan@usaid.gov

SUMMARY OF THE MPAG SESSIONS

Rethinking Malaria

Background: In the last few years, progress in reducing the global malaria burden has plateaued, after 15 years of progressive reductions that achieved an overall 50% reduction in burden and in deaths. The ongoing COVID-19 pandemic has further threatened the bold ambition of the WHO GTS, and has created new challenges for both human and financial resources and the delivery of essential malaria services. The COVID-19 pandemic has highlighted some important lessons for all public health challenges. Infectious diseases are once again at the forefront of global health, drawing attention both to the effects of structural inequities on the distribution of the burden of these diseases and their huge and long-lasting economic and social impact. As is the recognition that they can have huge and long-lasting economic and social impacts. Primary health care (PHC) and universal health coverage (UHC) are critical for dealing with future disease outbreaks and making progress on current challenges. However, delivery systems are often too weak to provide quality care to all those in need. Protecting health is a political choice, and political commitment is essential for scaling up UHC and tackling diseases that predominantly affect the poorest and most vulnerable. These groups need to be enabled to secure their health and the wellbeing of their communities.

Despite these challenges, the ambition and high-level strategy outlined in the GTS remain valid. However, to achieve these bold goals will require course correction, building on the HBHI approach. The urgency of the COVID-19 pandemic has further demonstrated the need for rethinking and adopting a wider perspective to address health systems and the broader determinants of health. The goal of the “Rethinking Malaria” effort is to bring together global stakeholders, with an emphasis on voices from those who deal with the disease on a day to day basis, and those most affected by the disease, to consider malaria challenges and opportunities in the context of COVID-19. The effort will build on recent compilations of knowledge, including the report of the Strategic Advisory Group on malaria eradication (SAGme), the Lancet Commission on malaria eradication within a generation, the MalERA Refresh, and the recent COVID-19-related documents on *Tailoring malaria interventions in the COVID-19 response* and the *Potential impact of health service disruptions on the burden of malaria*. The focus will be on three major topics: 1) malaria in governance of health systems; 2) malaria in integrated service delivery; and 3) malaria in training and capacity building.

Harvard University will serve as the convener, and other organizations will play key roles in defining the topics, identifying experts, and contributing to the knowledge base and topic discussions. WHO will coordinate a global consultative process, beginning with Africa, the continent with the highest burden. WHO will support countries to engage those who deal with malaria on a day-to-day basis. Their voices will be complemented by perspectives from political leadership, public health experts, scientists, implementers, academics, representatives of service users, development partners, leaders in non-

health sectors and other stakeholders. The process is expected to generate information on country-specific bottlenecks and guide the corresponding reform in how countries respond to malaria at national and subnational levels. The African regional consultations and inputs from other regions will contribute to a shared vision of the way forward for global malaria in a final report.

MPAG conclusions: MPAG supported the “Rethinking Malaria” agenda and suggested developing a clearer definition of what “rethinking” actually means. While the agenda acknowledges health system deficiencies, MPAG felt that it needs further thought to fully engage with the complexities and the structural inequities that underpin actions and responses to malaria. It requires an emphasis on how this “rethink” will continue to develop in response to local realities. MPAG agreed that COVID-19 has provided some important lessons for public health challenges, including highlighting the structural inequities of the burden of disease and the weaknesses of health services to achieve UHC and strengthen PHC. MPAG called out that while the response to the pandemic has increased the capacity of intensive care units, it has not given PHC strengthening the same priority as it should have. PHC strengthening requires updated technology, financial resources, and well trained and motivated human resources for all health problems. MPAG noted that this initiative will enable implementation of revisions to the high-level GTS that call for participatory analyses of health barriers and disparities to ensure equitable access to services and resilient health systems.

MPAG suggested rephrasing the intent to engage communities as: “Health systems actors need to be proactive in identifying and engaging with the most vulnerable, understanding and identifying local disease responses and resilience strategies, and working together to co-produce locally appropriate strategies”, while acknowledging that research is required to guide how best to do this. The Group cautioned that the most vulnerable cannot address the structural inequities themselves. This rethinking is an opportunity to change the narrative and to set responsibilities at different levels whereby structural inequities can be solved with the participation of the most vulnerable.

MPAG responded to the three major foci of this work:

- **Governance:** Rethinking malaria must go to all levels, i.e., communities and local authorities as well as high-level authorities. It should be a political priority for the country, meaning that enough financial resources must be allocated. It will be necessary to clarify how communities will be involved and how information will be used.
- **Integrated health service delivery:** Precision public health means that the right interventions should be addressed to the right population at the right time. A novel “game-changing” approach is needed that takes into account new strategies, maximizing impact, and new and updated technology.
- **Training and capacity building:** Capacity building is needed for health services, but should also be adopted in the multisectoral approach for the prevention and control of malaria and other health problems (integrated health service delivery). ‘Implementation’ is one of the three key areas identified, but it does include training in governance, leadership and management, which are all key to implementation at subnational levels. Training is required to facilitate planning and problem-solving at the subnational level through participatory research, co-creation and co-development.

Finally, MPAG highlighted the need to consider how the most vulnerable will be engaged in the process, as the unavailability of proper communication/internet facilities will be a constraint.

Clinical malaria – parasite density analysis and implications for diagnostic test specifications

Background: In malaria-endemic areas, a significant and varying proportion of the population can be infected with malaria parasites at any point in time, and often not associated with significant symptoms that lead them to seek care – often termed as asymptomatic malaria. Carriage of malaria parasites occurs frequently and the detection of malaria parasites in blood films (or antigens on rapid diagnostic tests [RDTs]) from a febrile individual does not necessarily indicate that the presence of malaria parasites is the cause of the fever or the symptoms leading to seek care. In clinical trials, case definitions for symptomatic malaria require the presence of fever together with a parasite density above a specific cut-off, and this is often dependent on age (as a function of naturally acquired immunity) and place (as a function of intensity of transmission). In clinical settings, the cut-offs for defining a malaria case are effectively based on the limits of detection of the diagnostic modality (i.e., microscopy, RDTs, PCR). The objective of this parasite density analysis was to evaluate different thresholds of parasite density that define clinical malaria and specifically: 1) to describe the distribution of parasite density among patients with malaria disease (defined by presence of fever or recent history of fever) that present at a health facility in different epidemiological settings and age groups in sub-Saharan Africa; 2) to describe the distribution of parasite density among symptomatic subjects presenting with fever or history of fever and asymptomatic subjects in cross-sectional surveys in different epidemiological settings and age groups in sub-Saharan Africa; and 3) to determine the attributable fraction of fever due to malaria, the sensitivity and specificity of different parasite density cut-off points, and implications for the use of existing diagnostic tools. This analysis did not address the relevance of asymptomatic parasitaemia to disease transmission, the health impact or natural history of undetected and/or asymptomatic parasitaemia, *P. falciparum* outside endemic areas of Africa, or *P. vivax*. The attributable fraction is the proportion of cases that are attributable to a risk factor, in this case, cases of fever due to malaria.

In 2009, WHO set minimum specifications for RDTs as being able consistently to detect 200 parasites per microliter (p/μL) with a false-positivity rate of less than 10%, based on data for health facilities or symptomatic subpopulations from cross-sectional surveys. The conclusion from the data reviewed was that RDTs with limits of detection around 200 p/μL will capture the majority of patients with clinical malaria/disease in endemic areas of Africa, but may miss some clinically relevant malaria infections (both *P. falciparum* and *P. vivax*) in south-east Asia, Papua New Guinea and South America. Since then, there has been increased interest in low-density infections and the potential role of more sensitive diagnostic tests for various use cases, including case management, surveillance, screening and elimination. WHO consultations between 2013 and 2017 upheld the use of microscopy and RDTs for clinical management. Highly/ultra-sensitive RDTs are available and recent price drops highlight the need to revisit whether clinical malaria cases are being missed with the current specifications and the clinical consequences of low density infections.

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