World Health Organization

WHO Malaria Policy Advisory Group (MPAG) meeting report

30 October–1 November 2023

Summary

The World Health Organization (WHO) convened the Malaria Policy Advisory Group (MPAG) for its 24th meeting held virtually and in person in Geneva on 30 October–1 November 2023. The key conclusions of MPAG to the Global Malaria Programme included the following:

- **Updates from the Global Malaria Programme.** The Director of the Global Malaria Programme gave an update on progress since the last MPAG meeting, including the development of the Global Malaria Programme operational strategy for the period 2024–2030; updated programme structure with five technical units; alignment within WHO on key technical issues, such as comparative efficacy assessment for vector control and the response to drug resistance in Africa; WHO certification of Belize as malaria-free in June 2023; and WHO recommendation of a second safe and effective malaria vaccine (R21/Matrix-M) in October 2023. He also presented the latest normative guidance and updates across all technical areas, and outlined the preparations for the World malaria report 2023.

- **Global Malaria Programme operational strategy 2024–2030.** The Global Malaria Programme operational strategy 2024–2030 outlines the Global Malaria Programme's role in implementing the *Global technical strategy for malaria 2016–2030* (GTS) *(1)* in coordination with all levels of WHO and within the malaria ecosystem. The operational strategy is aligned with WHO's Fourteenth General Programme of Work (GPW 14) and is accompanied by a description of concrete actions in operational plans; a monitoring and evaluation framework; and a resource mobilization strategy.

  MPAG supported the operational strategy and highlighted the need for coordination across the three levels of WHO (country, regional and headquarters) and between WHO departments and units, including the Prequalification (PQ) unit, to accelerate the timely, yet rigorous approval and implementation of new tools. MPAG emphasized the need for whole systems approaches, community engagement and capacity-building.

- **Update on malaria vaccines R21/Matrix-M and RTS,S/AS01, the Malaria Vaccine Implementation Programme (MVIP), and status of malaria vaccine roll-out.** The MVIP demonstrated a substantial impact of the RTS,S/AS01 vaccine, with a 13% reduction in all-cause mortality and a 22% reduction in hospitalizations for severe malaria. The vaccine improved the impact of other preventive measures (insecticide-treated nets (ITNs), seasonal malaria chemoprevention (SMC), indoor residual spraying (IRS)) being delivered in the pilot areas and was well received by the communities involved. There was no negative impact on the coverage of other routine childhood vaccines over time and no change in ITN use or care-seeking behaviour.

  WHO recommended the RTS,S/AS01 and R21-Matrix M malaria vaccines for the prevention of *Plasmodium falciparum* malaria in children living in malaria-endemic areas, prioritizing areas of moderate to high transmission. Decisions on expanding to low transmission settings should be considered at country level, based on the overall malaria control strategy, affordability, cost-effectiveness, and programmatic considerations, such as whether it would simplify delivery to include such areas.

  The demand for malaria vaccines continues to be high. Eighteen countries have been approved by Gavi, the Vaccine Alliance to receive support for malaria vaccine introduction.

  MPAG members congratulated GMP, IVB and their partners on achieving these milestones. MPAG members highlighted the importance of the MVIP findings on the implementation of a malaria vaccine using the routine Expanded Programme on Immunization (EPI) in each of the three pilot countries, and that the vaccine was well-received having no negative impact on uptake of other childhood vaccines, ITN use or care-seeking behaviour. Members were enthusiastic about the recommendation of both vaccines for use and strongly encouraged GMP, IVB and PQ to ensure that the high priority research recommendations are completed to fill knowledge gaps with respect to R21/Matrix-M. MPAG acknowledged that the decisions about apportioning vaccine doses of RTS,S and R21 to countries would be made by Gavi, with attention to country preference and other considerations, such as affordability and a country's ability to reach scale with one product. MPAG reiterated that vaccine implementation should be done in coordination with countries' national strategic plans.

- **Guiding principles for prioritizing malaria interventions in resource-constrained settings to achieve maximum impact.** The Global Malaria Programme has developed a document containing guiding principles for national malaria control programmes to prioritize malaria interventions in resource-constrained settings to achieve maximum impact. Prioritization is the process of selecting the most appropriate mixes of interventions for implementation and de-prioritizing others, considering financial constraints and programmatic feasibility. This process requires difficult choices to be made to minimize the negative impact of withholding some interventions, included in the national strategic plan.

  MPAG members recommended that the document should have a clear link to the guidance on subnational tailoring (SNT) and added that there was a need to invest in generating "good enough" data when there are challenges in obtaining accurate baseline data. Members recommended that case management should be a required capacity in all malaria endemic regions, as it is not the sole responsibility of the NMP, but should be in coordination with primary health care and community health workers to ensure this service is provided. They concluded by saying that more clarity is needed around the target audience and geographical settings.

  MPAG requested more information and will review a revised document after further consultation with additional national malaria programmes and WHO regional and country offices.

- **Update on SNT progress and challenges.** SNT is the use of local data and contextual information to determine the appropriate mix of interventions and strategies in a given area to achieve optimal impact on the transmission and burden of disease at the strategic level or within a specific resource envelope. The Global Malaria Programme provided an update on the status of implementation and findings.

  MPAG a that SNT be implemented in all regions where malaria is endemic, including those with low burden and low transmission. MPAG members emphasized that to sustain country-driven SNT processes, it is critical to invest in local systems and methodological innovations that generate the required data and capacity development. In addition, SNT should involve malaria-related sectors and local communities, as this is expected to enhance multisectoral collaboration and ownership of evidence-based decisions on selected priority malaria interventions. MPAG advised the Global Malaria Programme to ensure that the SNT approach considers both normal and crisis situations.

- **Comparative effectiveness in the context of the arrival of new vector control products.** The third technical consultation to assess the comparative efficacy of vector control products *(2)* informed updates to the vector control section of the WHO guidelines for malaria *(3)* and the WHO protocol for determining the comparative efficacy of vector control products *(4)*. An Organization-wide initiative was launched to enhance the alignment of the independent procedures for prequalification assessments and guideline development, with a view to accelerating the introduction of new public health products to the market. The evolution of the vector control evaluation process reflects WHO priorities related to alignment and shortened evaluation timelines.

  MPAG members welcomed the update on the process for new vector control products and congratulated the team on the development of comprehensive guidance on the methods required to assess the comparative effectiveness of second-in-class products. They noted that the processes outlined in the updated guidance is in agreement with wider initiatives across WHO to align the pre-qualification and guidelines processes as well as to minimise the time to market for new products. MPAG members raised the issue about limited testing capacity with experimental huts and that this might restrict the ability of studies to capture the natural variation in malaria transmission.

  MPAG members felt that durability, in terms of both the physical product and its efficacy, should be included in these evaluations.

- **Update on the "High burden to high impact" (HBHI) approach.** An evaluation of the HBHI approach was conducted to document the processes, lessons learned, best practices and challenges encountered in implementing HBHI in four countries. The evaluation showed that the implementation of HBHI has had varying degrees of success with respect to programme performance. Significant advancements have been made in the use of strategic information. Although political will has been expressed at the national level, this has not translated into additional resources and action.

  MPAG members agreed with concerns raised in the report that HBHI was viewed as a project rather than as an approach at the country level, and that there was a lack of knowledge of and involvement in the approach at the subnational level. MPAG members discussed the need for clarity around SNT, and the need for strategies to address the introduction of new tools, such as vaccines, and their integration with the HBHI approach. MPAG encouraged the Global Malaria Programme to provide operational guidance that more clearly defines the HBHI approach and how it can be adopted and adapted within high-burden countries.

- **Updates to the WHO guidelines for malaria: tafenoquine recommendation and glucose-6-phosphate dehydrogenase (G6PD) diagnostics.** The Global Malaria Programme will convene two Guideline Development Group (GDG) meetings in November 2023. The GDG on malaria chemotherapy will review the evidence and generate recommendations on tafenoquine and primaquine as anti-relapse therapy for *P. vivax* and *P. ovale*, and on single low-dose primaquine to reduce the transmissibility of *P. falciparum*. The GDG on malaria diagnostics will review the evidence and generate recommendations on near-patient diagnostic tests for G6PD deficiency.

  MPAG concluded that there is an urgent need to finalize the recommendation for the use of tafenoquine for anti-relapse treatment of *P. vivax*, and Prequalification approval of a suitable G6PD test and the associated guidelines for use. MPAG members expressed concern about G6PD tests specifically for remote areas and requested that the GDG on diagnostics pay attention to this issue. MPAG noted that it would be appropriate to review additional evidence on primaquine dosing, as new reports have emerged.

- **Update on antimalarial drug resistance in Africa.** The *Strategy to respond to antimalarial drug resistance in Africa (5)* was launched in November 2022. *PfKelch13* (K13) mutations associated with delayed clearance after treatment with an artemisinin-containing treatment are emerging and spreading in the Horn of Africa and East Africa, with artemisinin partial resistance confirmed in four countries in Africa: Eritrea, Rwanda, Uganda and the United Republic of Tanzania. WHO is convening a regional stakeholder meeting to align on intervention priorities to support countries responding to resistance, and a meeting on surveillance of drug efficacy and resistance for countries in East Africa and the Horn of Africa. WHO is working with countries to support data validation to facilitate action.

  MPAG considered the situation of antimalarial drug resistance in Africa to be urgent, as it poses a major threat to malaria treatment and control efforts across the continent, and called for an immediate plan of action. MPAG highlighted the need for additional resources to respond to this threat. In addition, it highlighted the critical need for more data from the surveillance networks across Africa.

- **Update on the Mekong Malaria Elimination programme.** Over the past 10 years, with the support of the Mekong Malaria Elimination programme, countries in the Greater Mekong subregion have made remarkable progress towards their collective goals of eliminating *P. falciparum* by 2023 and eliminating all human malaria species by 2030. However, the continued unstable political situation in Myanmar has resulted in an overall increase in cases across the subregion. Reaching the unreached populations, particularly remote and marginalized communities, is vital for malaria elimination. This requires a comprehensive, tailored and participatory approach that considers social, economic and political factors. Planning for the prevention of re-establishment of malaria is essential to fulfil the criteria for certification of malaria-free status.

  MPAG recommended that the WHO Regional Office for South-East Asia and Regional Office for the Western Pacific work with Chinese authorities, who can share the lessons learned from their successful within-country malaria elimination campaign. MPAG noted the very encouraging finding that artesunate-mefloquine is maintaining its efficacy in Cambodia after five years. The Group strongly supported the Mekong Malaria Elimination programme's increased emphasis on radical cure coverage to eliminate the *P. vivax* liver stage reservoir and its work with local teams to eliminate malaria.

Background

The World Health Organization (WHO) convened the Malaria Policy Advisory Group (MPAG) for its 24th meeting held virtually and in person in Geneva on 30 October–1 November 2023. MPAG convenes twice annually to provide independent strategic advice to WHO on technical issues related to malaria control and elimination. The hybrid meeting included the participation of MPAG members and observers joining either in person at WHO headquarters or remotely via a virtual conferencing platform. Over the course of the two days of open meetings, 19 MPAG members, more than 20 national malaria programme managers, the WHO Secretariat, and 579 registered observers discussed updates and progress in the work areas presented. MPAG discussed conclusions and advice to the Global Malaria Programme in a closed session on day three.

All 19 MPAG members participating in the meeting updated their Declarations of Interest in advance of the meeting, which were assessed by the WHO Secretariat; 13 members reported interests. The full report on members' Declarations of Interest was published two weeks before the meeting and is available on the meeting website. No MPAG members reported conflicts of interest specifically related to the agenda topics. It was assessed that all members could fully participate in all sessions.

Overview of the MPAG sessions

Updates from the Global Malaria Programme

The Director of the Global Malaria Programme reminded participants of the Global Malaria Programme's vision – a world free of malaria – and its mission, which is two-fold: to support all Member States in implementing the GTS; and to promote effective partnerships with malaria stakeholders. He also shared the Global Malaria Programme's four core functions:

- to play a leadership role in the malaria response, effectively supporting Member States and rallying partners to reach universal health coverage (UHC) and achieve the GTS goals and targets;
- to shape the research agenda and promote the generation of evidence to support global guidance for new tools and strategies to achieve impact;
- to develop ethical and evidence-based global guidance on malaria, with effective dissemination, to support adoption and implementation by national malaria programmes and other relevant stakeholders; and
- to monitor and respond to global malaria trends and threats.

The Director highlighted key achievements in his first 100 days as Director, including the approval of a new programme structure with five technical units; recruitment of a new programme manager; development of the new operational strategy for the period 2024–2030; and alignment within WHO on key technical issues, such as comparative efficacy assessment for vector control and the response to drug resistance in Africa.

The Director highlighted key moments in the malaria response since the last MPAG meeting, notably the WHO certification of Belize as malaria-free in June and the WHO recommendation of a second safe and effective malaria vaccine (R21/Matrix-M) in October. He shared the Global Malaria Programme's latest meeting reports, normative guidance and updates across all technical areas, including progress to date in 2023 and priorities for the next quarter.

The Director shared the programme's plans for the upcoming release of the World malaria report, which for the first time will include a dedicated chapter on malaria and climate. The report will be launched at the 28th meeting of the Conference of the Parties

to the United Nations Framework Convention on Climate Change (COP28) in Dubai in early December.

Finally, the Director informed participants that WHO will host a high-level meeting of Ministers of Health and Finance in March 2024, aimed at strengthening political and financial commitments for accelerated malaria responses in HBHI countries.

Global Malaria Programme operational strategy 2024–2030

Background

Global malaria progress has stalled in recent years, and a "business as usual" approach will take countries and their development partners further off course. Recognizing that getting back on track will require a pivot in the malaria response, the Global Malaria Programme has developed a departmental operational strategy for the period 2024–2030.

While the operational strategy focuses on the Global Malaria Programme's role, it also acknowledges the importance of a concerted effort across the malaria ecosystem to accelerate progress towards the GTS 2030 targets. The operational strategy is therefore fully aligned with the GTS and WHO's GPW 14.

The strategy reflects inputs from countries, partners and WHO colleagues, who have contributed to a better understanding of the root causes of stalled progress. Their inputs have enabled the Global Malaria Programme to identify how the department can better deliver on its mandate to address current challenges and maximize new opportunities.

The operational strategy focuses on four strategic objectives: norms and standards; new tools and innovation; strategic information for impact; and leadership. A fifth cross-cutting pillar, context-based country support, completes the objectives. The strategy will be accompanied by detailed operational plans outlining specific activities and a results framework to provide greater transparency and accountability.

MPAG conclusions

MPAG congratulated the Global Malaria Programme Director on the development of the Global Malaria Programme operational strategy, with its focus on norms and standards; new tools and innovation; strategic information for impact; and leadership to accelerate the implementation of new guidelines at country level. MPAG members noted the need for coordination across the three levels of WHO (headquarters, regional offices and country representatives). The coordination between WHO departments and units, including the Prequalification unit, to accelerate the timely, yet rigorous approval and implementation of new tools was highlighted as a major strength. Proactive engagement with drug, vaccine, diagnostic and vector control private sector stakeholders was cited as an additional strength. MPAG members raised several issues for consideration, including the need to analyse root causes from a systems perspective rather than in individual silos; engage the community; provide education and capacity-building; address the issue of collective resources to maximize impact; improve the focus on data quality; ensure capacity in dealing with emerging biological threats; and provide explicit support for countries in situations of crisis.

Update on malaria vaccines R21/Matrix-M and RTS,S/AS01, the Malaria Vaccine Implementation Programme (MVIP), and status of malaria vaccine roll-out

Background

The MVIP is coming to a close in December 2023, with more than 2 million children having received over 6 million doses since the start of vaccination in 2019. The immunization programmes in all three pilot countries achieved reasonably high

coverage of the first three doses, even in the midst of the coronavirus disease (COVID-19) pandemic, natural disasters, labour disputes and supply issues with other EPI vaccines. Coverage of the fourth dose was less than optimal. In the 46 months following vaccine introduction, the MVIP demonstrated a substantial impact of the RTS,S/AS01 vaccine, with a 13% reduction in all-cause mortality excluding injury (rate ratio: 0.87; 95% CI: 0.78–0.98) and a 22% reduction in hospital admissions for severe malaria (0.78; 95% CI: 0.64–0.96). This impact was measured in children who were age-eligible to receive the vaccine (~63% to 75% dose-three coverage, 33% to 54% dose-four coverage), and demonstrates added benefit on top of that seen with good ITN use and good access to care in these areas. The MVIP Data Safety and Monitoring Board's review of safety data collected across this large pilot implementation found no safety concerns regarding the use of RTS,S/AS01 in children. This landmark malaria vaccine effectiveness study, carried out in the context of routine EPI delivery, is the first to demonstrate a decrease in all-cause mortality in children. The vaccine added to the impact of other preventive measures (ITNs, SMC, IRS) being delivered in the pilot areas and was well received by the communities involved. There was no negative impact on the coverage of other routine childhood vaccines over time and no change in ITN use or care-seeking behaviour in areas where the RTS,S/AS01 vaccine was delivered, relative to the comparator areas. On 2 October 2023, following a joint evidence review by MPAG and the Strategic Advisory Group of Experts on Immunization, WHO recommended a second malaria vaccine, R21/Matrix-M, for the prevention of *Plasmodium falciparum* malaria among children living in malaria-endemic areas, prioritizing areas of moderate to high transmission. Decisions on expanding either RTS,S or R21/Matrix-M to low transmission settings should be considered at country level, based on the overall malaria control strategy, affordability, cost-effectiveness, and programmatic considerations, such as whether it would simplify delivery to include such areas.

Prequalification review for R21/Matrix-M was initiated in early 2023. The recommendation cites favourable data on efficacy and safety and emphasizes several high-priority areas for further monitoring and research. Initial modelling suggests that R21/Matrix-M, like RTS,S/AS01, can have high public health impact across a range of transmission settings and favourable cost-effectiveness. No head-to-head trials have directly compared the efficacy of the two vaccines. Therefore, based on currently available data, it is not possible to determine whether one vaccine has greater efficacy and/or duration of protection than the other. The clinical trials of each vaccine evaluated different vaccine administration schedules, were conducted in different transmission settings and had different follow-up periods. However, given that R21/Matrix-M is similar to RTS,S/AS01, in that they target the same antigen and use similar vaccine constructs and adjuvants, it is likely that R21/Matrix-M will have a similar public health impact. The choice of product to be used in a country should be based on product characteristics and programmatic needs, vaccine supply availability, the likelihood of being able to scale up with a single product, and long-term affordability considerations.

The demand for malaria vaccines continues to be high. Since Gavi opened a funding window in mid-2022, 18 countries have been approved to receive support for malaria vaccine introduction. Of these, 12 countries (including the three pilot countries involved in the MVIP) have been allocated the limited number of available doses of RTS,S/AS01 vaccine for introduction beginning in Q1 2024. Contingent on WHO prequalification, it is expected that R21/Matrix-M will be available to countries in mid-2024. It is likely that RTS,S/AS01 and R21/Matrix-M will be available in a two-vaccine market, which is expected to substantially increase supply and lower costs. At least 28 countries in Africa have expressed interest in introducing a malaria vaccine, and it was reported that Gavi is working with other partners to plan for a vastly improved supply landscape for malaria vaccines. The availability of two vaccines (RTS,S/AS01 and R21/Matrix-M) will enable more countries to introduce and scale up malaria vaccines.

Questions remain about the use of malaria vaccines in low transmission settings (impact was shown in low transmission settings for both RTS,S/AS01 and R21/Matrix-M, but additional mathematical modelling has been recommended); the contexts in which a fifth dose might be needed (other than in areas of highly seasonal transmission); and the effectiveness of different delivery strategies. Although high impact has been measured

with the introduction of RTS,S/AS01, the impact of the R21/Matrix-M vaccine on severe malaria or mortality has yet to be shown; these outcomes should be evaluated post-licensure. An additional important question is related to the effectiveness and duration of protection of R21/Matrix-M in areas of high perennial malaria transmission. Gavi is considering the programmatic, technical and financial aspects of all of these issues.

MPAG conclusions

MPAG members congratulated the Global Malaria Programme, the Immunization, Vaccines and Biologicals department and their partners on achieving these milestones. The demonstrated impact of RTS,S/AS01 on all-cause childhood mortality during the MVIP is a landmark for the field. MPAG members highlighted the importance of the MVIP findings regarding the implementation of a malaria vaccine using routine EPI delivery in each of the three pilot countries, and that the vaccine was well received with no negative impact on the uptake of other childhood vaccines, ITN use or care-seeking behaviour. MPAG was of the view that these findings should be more broadly distributed, including the lessons learned, to inform other countries as they roll out RTS,S/AS01 and/or R21/Matrix-M. The MVIP resolved lingering issues related to RTS,S/AS01 in the context of carefully documented delivery to millions of children, demonstrating that vaccination can be scaled up through real-world health systems. Members also recommended that cost-effectiveness studies be updated based on the reduction in all-cause mortality recorded by the MVIP.

MPAG members were enthusiastic about the recommendation for use of the R21/Matrix-M vaccine, based on discussions in the closed session and during the combined MPAG/Strategic Advisory Group of Experts on Immunization review in September. MPAG Members were enthusiastic about the recommendation of both vaccines for use, and strongly encouraged the Global Malaria Programme, the Immunization, Vaccines and Biologicals department and the Prequalification unit to ensure the implementation of the high-priority research recommendations to address the knowledge gaps with respect to R21/Matrix-M. These include:

- immunological studies of co-administration with other childhood vaccines;
- post-licensure evaluation studies of vaccine effectiveness in high perennial transmission settings that are not represented in the Phase 3 trial;
- monitoring of risk of malaria rebound and further data on severe malaria and mortality as part of the ongoing Phase 3 trial and four years of follow-up (already planned by the developer), including the monitoring of post-boost vaccine efficacy;
- post-licensure monitoring of R21/Matrix-M safety in infants and young children, including the occurrence of febrile seizures and mortality; monitoring of mortality may be most easily achieved in areas where there is a demographic surveillance system in place;
- evaluation of vaccine efficacy against severe malaria (e.g. a case–control study);
- evaluation of vaccine impact on mortality using available systems, e.g. health and demographic surveillance system, community mortality surveillance, case–control study; and
- interchangeability studies on heterologous schedules with RTS,S/AS01 and R21/Matrix-M.

In addition, MPAG supported the recommendation of the MPAG/Strategic Advisory Group of Experts on Immunization working group for additional cost-effectiveness analyses based on R21/Matrix-M data from the Phase 3 trial, including by additional modelling groups. MPAG also supported the recommendation to form a team at WHO to monitor the implementation and results of these high-priority research activities and requested an annual briefing on the progress and findings.

MPAG acknowledged that the decisions on apportioning the vaccine doses of RTS,S/AS01 and R21/Matrix-M to countries would be made by Gavi, with attention given to country preferences and other considerations, such as affordability and a country's ability to reach scale with one product. In addition, MPAG recognized the advantages of a potential two-vaccine market, particularly in terms of supply and price, and encouraged WHO and its partners to track producers' supply and pricing commitments that will shape that market. MPAG reiterated that vaccine implementation should be done in coordination with countries' national strategic plans.

Guiding principles for prioritizing malaria interventions in resource-constrained settings to achieve maximum impact

Background

In response to ever increasing financial constraints, the WHO Global Malaria Programme and regional offices, in consultation with Member States and technical partners, have developed guidance for national malaria control programmes, setting out the guiding principles for prioritizing interventions in resource-constrained settings to achieve maximum impact. The document was refined following reviews and inputs received from the managers of the national malaria control programmes of Cameroon, the Democratic Republic of the Congo, Nigeria, Rwanda and Zambia, the African Leaders Malaria Alliance, the Bill & Melinda Gates Foundation, the Global Fund to Fight AIDS, Tuberculosis and Malaria, the RBM Partnership to End Malaria and the United States President's Malaria Initiative.

The need for this document became evident when grant applications by national malaria control programmes to the Global Fund Cycle 7 in windows 1 and 2 (submitted in Q1–Q2 2023) faced a significant funding gap compared to Global Fund country allocations. Several countries requested interventions to be frontloaded in years one and two (2024–2025), leaving gaps in essential services in year three (2026). The estimated malaria funding gap is approximately US$ 1 billion to sustain essential services (case management in the public sector, ITNs in moderate to high transmission areas and SMC). Subsequent adjustments in funding to access more effective medicines for malaria case management have led to bigger funding gaps for vector control and SMC in 2026.

The guiding principles align with the GTS and with Sustainable Development Goal 3. The principles promote the ambition of leaving no one behind and ensuring access to effective malaria interventions to all those in need. Prioritization is the process of selecting the most appropriate mixes of interventions for implementation and de-prioritizing others, considering financial constraints and programmatic feasibility. This process requires difficult choices to be made to minimize the negative impact of withholding some interventions included in the national strategic plan. This differs from optimization, which ensures that the strategies and interventions deployed will achieve maximum impact with the most efficient use of available resources.

The first part of the document outlines the basic principles of prioritization, grounded in primary health care and UHC, patient-centredness (community-focused), self-determination, accessibility, equity, quality, empowerment, intersectoral collaboration, value and sustainability, accountability and transparency. The document proposes that prioritization must be informed by the baseline (historical) transmission intensity and disease burden in a given area, before preventive interventions were scaled up, to determine the level of risk of resurgence and potential impact of the decision to remove the interventions. Prioritization of malaria interventions should be consistent with the principles of country ownership, cost-effectiveness, financial risk protection, political acceptability and programmatic realities.

In the face of limited resources, the primary objective is to prevent and minimize malaria-related deaths. This is assured by providing access to early diagnosis and

effective treatment of all malaria cases, irrespective of the malaria transmission intensity. Providing prompt access to malaria diagnosis and treatment by maintaining existing services across all levels of the health care delivery system, including at the community level, should be prioritized, and guaranteed for all as a basic human right. Scaling back access to early diagnosis and treatment is not an option under any level of financial constraint.

The guiding principles emphasize the importance of continuing to invest in improvements to surveillance and the quality and effectiveness of the prioritized interventions. These investments should not be reduced as part of prioritization, as these are essential to achieving impact. The document provides guiding principles on vector control, including ITNs and large-scale implementation of IRS, expansion of case management to the community level and in the private sector, ongoing chemoprevention interventions (intermittent preventive treatment of malaria in pregnancy and SMC), the deployment of malaria vaccines, and new chemoprevention interventions (geographical or age expansion of SMC, community deployment of intermittent preventive treatment of malaria in pregnancy, perennial malaria chemoprevention, post-discharge malaria chemoprevention and intermittent preventive treatment of malaria in school-aged children).

The document concludes with a reminder that prioritization is an iterative process that should be continuously revised as costs and funding opportunities and malaria epidemiology change over time, programme performance shows changing requirements, new tools and knowledge become available, and new threats emerge. Mobilizing additional resources is a continuous effort that should be pursued during and after prioritization planning, based on the evidence-informed national strategic plan.

The document on guiding principles for the prioritization of interventions is based on current WHO guidance and will be revised following the review and inputs of MPAG and further consultations with the main target audience: national malaria control programme managers and their technical and development partners. The document will be updated on an annual basis as new WHO guidance is developed.

MPAG conclusions

MPAG congratulated the Global Malaria Programme for presenting the principles for prioritizing malaria interventions in resource-constrained settings. Members were of the view that this is an extremely important and timely document that emphasizes the need to use limited resources in a way that achieves the highest possible impact on the malaria burden, with the priority being prevention or reduction of malaria-related deaths. This document is an important first step in a longer process and should be regularly updated to remain relevant to country needs. MPAG noted the limited feedback received so far from the community level and national malaria programmes, highlighting the importance of consulting as many national malaria programmes as possible, collecting their views and modifying the document accordingly. This will also increase country ownership.

Key points raised during discussion for additional consideration by the Global Malaria Programme included the following:

- **Alignment with SNT guidance:** It was noted that SNT is closely related to this topic, in that information provided by the SNT will be used by countries in prioritizing interventions both for domestic and international funding. The two documents should be linked or perhaps merged. MPAG was concerned, however, that there may be insufficient local capacity for SNT and this gap needs to be addressed.

  Furthermore, it is important to build the capacity of countries to move from the use of baseline/historical data to collect and use of current data. MPAG acknowledged the tension between the need to provide guidance and the danger of being too prescriptive, and reiterated the importance of ensuring that the document is not perceived as prescriptive.

- **Surveillance:** MPAG noted that the importance of surveillance and the quality of available data should be emphasized. Surveillance should be a core activity, regardless of the resources available. National capacity for surveillance should be strengthened to enable SNT.
- **Baseline data needs:** MPAG noted that the document states that prioritization relies on baseline information (with the baseline period defined as the time before interventions were scaled up). However, it may be challenging to have accurate baseline data, particularly in resource-constrained settings, which might result in flawed assumptions and thus suboptimal decisions. It is therefore essential to emphasize the need to invest in generating "good enough" data to inform the optimization of interventions. The definition of "good enough" data must be clear. Baseline figures should also align with country programmatic timelines, such as those used for the malaria programme review and the national strategic plan.

  Case management should be understood as a required capacity in all regions where malaria transmission occurs. MPAG members noted, however, that this is not the sole responsibility of the national malaria programme but should be coordination with primary health care and community health workers to ensure that these services are provided.
- **Capacity and support needs:** MPAG was of the view that while the available interventions are well described, many countries may not have the required expertise to make decisions on the different options without external expert input, e.g. from a regional advisor or the Global Malaria Programme. As resource-constrained countries are more likely to have limited vector surveillance data, it is paramount to increase capacity in these countries for undertaking vector surveillance. WHO needs to evaluate the present capacity to identify gaps and to encourage capacity-building to fill the gaps. Finally, national malaria programmes have an important responsibility to decide what interventions to prioritize and what regions to target. They should be supported in making such difficult decisions, particularly when it concerns the scale-back of interventions. Documenting such decisions will be extremely important, as these could be taken as a reference for future decisions and provide lessons learned for other national malaria programmes. Increased and more systematic training of national malaria programmes in leadership and management skills has often been overlooked, but will be critical for optimal decision-making.
- **Clarity on target audience and geographical settings:** MPAG noted that the document attempts to be applicable to all settings. However, it is mostly tailored to the African context and this should be stated more clearly. In addition, urban settings are complex and there may be a need to deprioritize vector control in specific urban settings. Although the document does not aim to guide the optimal combination of intervention mixes, it is important to outline the scenarios or types of decisions that countries might face.

  MPAG indicated that it would review a revised document after the Global Malaria Programme has held further consultations with additional national malaria programmes and addressed the issues raised by MPAG and other stakeholders.

Update on SNT progress and challenges

Background

SNT is the use of local data and contextual information to determine the appropriate mix of interventions and strategies in a given area to achieve optimal impact on the transmission and burden of disease at the strategic level or within a specific resource envelope. SNT can also be used to inform how new tools can be most effectively

integrated within previously planned mixes of interventions, or for dynamic resource mobilization as additional funding opportunities become available.

The following essential steps are involved in the development and monitoring of prioritized malaria control and elimination programmes, as implemented under the SNT process:

1. Establish a national SNT team.
2. Determine the criteria for tailoring interventions.
3. Stratify malaria risk and its determinants to inform the criteria.
4. Identify the areas eligible for each intervention according to the specified criteria (step 2) and informed by the stratification process (step 3), leading to the development of various scenarios of intervention mixes.
5. Project the impact of these scenarios and refine the plan.
6. Select the final mix of interventions and strategies through a consensus-based approach informed by the evidence.
7. Cost the resulting strategic plan and trigger resource mobilization.
8. If the resources are insufficient to cover the costed strategic plan, proceed to the rational prioritization of investments to maximize impact through further use of stratification of determinants and mathematical modelling.
9. Plan to monitor the impact of the deployed interventions so that the response can be honed over time and resources reprioritized as needed.

Since 2018, the Strategic Information and Response Unit of the Global Malaria Programme has worked in close collaboration with WHO regional and country offices to respond to requests from more than 30 countries in the WHO African, Eastern Mediterranean and South-East Asia Regions for support in the implementation of the SNT process, specifically to inform strategic planning, resource mobilization, funding requests, budget negotiations, optimization of intervention implementation, and so on, for single or multiple interventions. The Strategic Information and Response Unit also organized a series of malaria epidemiological stratification workshops in July and September 2023, in which 22 national malaria programme staff and local universities participated. A third workshop is planned for the end of November 2023, in collaboration with the WHO Regional Office for Africa.

In 2024, the Strategic Information and Response Unit intends to develop an SNT implementation manual that will provide the information required for national malaria programmes and partners to follow the process recommended by WHO. The finalization of the guiding principles for prioritization document will be required to ensure that the analytical products recommended in the manual to inform strategic and prioritization decision-making are adequate and aligned with WHO recommendations. Further convenings of the Malaria Strategic Information Technical Advisory Group (MSI-TAG) will be planned to provide an independent review of the manual and additional aspects related to surveillance, monitoring and evaluation, and use of data. The Strategic Information and Response Unit will also work very closely with the WHO regions and the Precision Public Health Metrics unit at the WHO Regional Office for Africa to collectively respond to countries' requests for SNT support, and continue to engage with national malaria programmes and partners to reinforce the development of local capacity to implement the SNT process at country level.

MPAG conclusions

Overall, MPAG considered that the processes and principles of SNT were well defined, but needed to be fully aligned with the principles for prioritizing intervention mixes presented in the previous session. SNT is rightly anchored on using local data for decision-making. Decentralization that drives decision-making and resource allocation to state/province and municipal levels requires the political will of local authorities to implement interventions and strategies for malaria elimination. SNT should be

implemented within the framework of the primary health care approach and integrated into the health system of the country where it will be applied. SNT includes community and civil society involvement, as well as a multisectoral approach for the implementation of interventions for elimination. SNT implies that strategies and interventions may vary from one area to another, since different determinants of health also vary across geographical areas.

MPAG was pleased to see that country ownership of SNT was high, with broad participation and feedback by all stakeholders. MPAG members recommended that SNT should be implemented in all regions where malaria is endemic, including those with low burden and low transmission, e.g. Latin American countries such as the Bolivarian Republic of Venezuela, Brazil, Colombia and Peru. Despite low numbers of cases, these countries still face significant challenges in achieving malaria elimination. MPAG also queried whether SNT could be used in unstable humanitarian settings and whether the process needs to be adapted to accommodate information gaps in this context. Moreover, it is important to emphasize that to sustain country-driven SNT processes, it is critical to invest in local systems and methodological innovations that generate the required data and capacity development.

MPAG members agreed that the SNT document explains that SNT should be used to guide not only disease-specific interventions, but also programmatic and health system actions that will increase the effectiveness of malaria control interventions. The document also states that "WHO is moving away from declaring some interventions as core and others as complementary...". This was seen as somehow contradictory to the "principles for prioritizing interventions" session, in which core interventions were presented as essential, to be introduced before adding other interventions. Both guidance documents need to be integrated more holistically to ensure clarity around the key messages for national malaria programmes. SNT should be considered for external and domestic resource mobilization as well as to guide elimination activities.

MPAG recommended that the SNT team involve malaria-related sectors and local communities to enhance multisectoral collaboration and ownership of evidence-based decisions on selected priority malaria interventions. MPAG advised the Global Malaria Programme to ensure that the SNT approach considers both normal and crisis situations.

Comparative effectiveness in the context of the arrival of new vector control products

Background

Since the MPAG meeting in April 2023, the Global Malaria Programme has convened its third technical consultation on 5 and 9 June 2023 to assess the comparative efficacy of vector control products. The associated meeting report was published on 20 September 2023 *(2)*. The meeting outcomes and recommendations formed the basis for an update to the vector control section of the WHO guidelines for malaria, published on 16 October 2023 *(3)*, and revision of the WHO protocol for determining the comparative efficacy of vector control products *(4)*, and informed further evolution of the vector control evaluation process. The latest comparative efficacy meeting focused on the assessment of four products – two pyrethroid-piperonyl butoxide (PBO) nets, one pyrethroid-chlorfenapyr net, and one IRS product – to determine whether they should be considered as covered under existing WHO recommendations, or whether it was necessary to extend existing recommendations or develop new ones. Based on the demonstration of non-inferiority to the first-in-class products of all the products assessed, WHO determined that all three ITNs were covered by the existing recommendation for the intervention class to which they belong, and that the IRS recommendation for malaria should be extended to include the insecticide broflanilide.

In addition to providing the evidence base required to inform guidelines discussions, the technical consultation proposed a number of methodological improvements. A key

challenge identified was the use of a fixed odds ratio of 0.7 as the non-inferiority margin, which makes it nearly impossible to demonstrate non-inferiority to an extremely well performing active comparator. This could lead to products that perform well overall being classified as inferior, even though the actual difference in performance (in this case, mortality) between the candidate product and the active comparator is small and likely to be of no operational relevance. To avoid this potential situation, WHO will adopt the recommendations from the technical consultation to modify the methodology in a way that preserves the use of non-inferiority as the sole decision-making approach and the use of an odds ratio, but introduces an odds ratio for the non-inferiority margin that varies depending on the percent mortality achieved by the first-in-class product. The updated protocol, which will be published before the end of 2023, will reflect this methodological evolution, along with other advice provided at this consultation and the previous meeting on comparative efficacy in 2021, and practical experiences gained during implementation of studies in recent years. To facilitate implementation of the required studies and analysis, WHO has drawn on support from Imperial College London and the London School of Hygiene and Tropical Medicine to develop a tutorial and statistical analysis packages that have been made available online, and an educational video.

In response to MPAG's repeated guidance to WHO to introduce comparative efficacy assessments for all vector control products other than first-in-class ones (i.e. those with data on epidemiological impact) and to ensure full coordination of the evaluation processes across the organization, the Global Malaria Programme has worked closely with the Regulation and Prequalification department's Vector Control Product Assessment Team and the Guidelines Review Committee to develop an updated flowchart that now incorporates the generation, assessment and use of comparative efficacy data. An advanced draft of the flowchart has been presented to MPAG and will form part of an update to the document *Norms, standards and processes underpinning development of WHO recommendations on vector control (6)* and its annex on roles and responsibilities. WHO informed participants that an organization-wide initiative has been launched to enhance the alignment of the independent procedures for prequalification assessments and guidelines development, with a view to accelerating the introduction of new public health products to the market. The initiative is led by the Science Division and the Regulation and Prequalification department. The Global Malaria Programme is part of the working group. The evolution of the vector control evaluation process fully reflects organizational priorities related to alignment and shortened evaluation timelines.

MPAG conclusions

MPAG members welcomed the update on the process for new vector control products and congratulated the team on the development of comprehensive guidance on the methods required to assess the comparative efficacy of second-in-class products. They noted that the processes outlined in the updated guidance are in agreement with the wider initiatives across WHO to align the prequalification and guidelines processes, and to minimize the time to market of new products. MPAG members noted the complexity of the process, but were reassured that the current timeline from portfolio submission to listing was within 12 months. Members felt it would be helpful to include the expected timeline in the flowchart to reassure manufacturers.

MPAG members raised the issue of limited testing capacity with experimental huts, which might restrict the ability of studies to capture the natural variation in malaria transmission. While there is a recommendation to undertake at least two studies in different geographical areas, there did not seem to be a recommendation to undertake second-in-class comparative studies in the same location as the first-in-class studies. MPAG members also raised the question of whether future normative guidance might consider vector control products to be recommended with limited scope – for example, pertaining to particular housing structures or specific ecological zones.

MPAG members noted that studies of the efficacy of vector control products frequently measure a wide range of entomological indicators and noted that the prequalification process currently assesses all of those submitted. As not all of these measures will necessarily reflect the efficacy of the products, it would be helpful to provide a listing of primary and secondary outcomes across the full range of vector control products (as has already been detailed for ITNs). It was also noted that the comparative efficacy assessment for IRS included a residual efficacy component and the ITN evaluation included an artificial aging assessment. MPAG members felt that durability, in terms of both the physical product and its efficacy, should be included in these evaluations. Furthermore, questions were raised by several observers regarding plans for a framework for post-market surveillance and monitoring to inform the community on issues of durability in real-world settings.

Update on the "High burden to high impact" (HBHI) approach

Background

In 2018, WHO and the RBM Partnership launched the HBHI approach in the highest burden countries to reignite the pace of progress in the global fight against malaria *(7)*. The approach is led by 11 countries that, together, account for approximately 70% of the global malaria burden. HBHI is an intensified approach to reduce malaria mortality and morbidity in the countries hardest hit by the disease and bring the disease trend in these countries back on track towards achieving the GTS targets. It is achievable to decrease malaria mortality in these countries with the existing systems and tools, while intensifying preventive interventions. However, this requires translating the political will into optimization of health systems, investment in community health workers, and strong leadership in realizing multisectoral action. The approach is characterized by packages of malaria interventions that are optimally delivered through appropriate channels, including through a strong foundation of primary health care.

An evaluation was conducted to document the processes, lessons learned, best practices and challenges encountered in implementing the HBHI approach and to address gaps in the approach in Cameroon, Ghana, Mali and Niger in order to better adapt and expand the approach to other countries. The outcomes of this evaluation in the four countries are complementary to the findings from the evaluation in the other six HBHI countries in Africa, which was completed in early 2022. Specifically, the objectives were to:

- evaluate the country-level outcomes of applying the HBHI approach, identify best practices and barriers to success, and suggest course corrections for future actions;
- evaluate the global-level processes supporting the HBHI approach; and
- consolidate lessons learned and best practices and set recommendations on the use of the lessons learned in the expansion of the HBHI approach to more malaria-endemic countries.

The evaluation showed that implementation of the HBHI approach has had varying degrees of success in improving programme performance at the country level. Notably, there have been significant advancements in certain areas, particularly in strategic information and political will. In these areas, dedicated resources, time and effort have yielded obvious improvements. The quality of data has improved, and the quality of national strategic plans has also been enhanced, enabling resource mobilization and clarity in deployment of the interventions. The approach's overall impact has been a broader recognition of the importance of data and SNT of interventions, reflecting positive outcomes.

The extent of progress, however, has been slightly constrained by challenges related to the effects of the COVID-19 pandemic, inadequate coordination, inadequate resources, widespread and persistent conflicts in many of the HBHI countries, the need to develop better guidance and policies locally, and the lack of ability to effectively engage other sectors and critical non-health stakeholders in the fight against malaria. Translating the expression of political will into an increase in domestic financing and investment in the fight against malaria has also proven to be a bottleneck. Roll-out of the HBHI approach has still not moved beyond the national level in many of the HBHI countries, with a general lack of awareness observed at the subnational level.

Significant advancements have been made in the use of strategic information. Although political will has been expressed at the national level, this has not translated into additional resources and action.

While the HBHI approach has played a significant role in improving malaria programme performance in countries, measuring its impact can be challenging without defined performance metrics. To determine the success of the HBHI approach, a monitoring and evaluation framework should have been included and clear metrics established a priori to assess the effectiveness of the approach.

MPAG conclusions

MPAG discussed the update on HBHI and recognized the achievements of HBHI implementation and the positive activities under way. Members considered the strategic shift in the HBHI approach towards accelerating mortality reduction to be a positive move. However, they emphasized the importance of enhancing prevention to reduce transmission, instead of focusing solely on stopping deaths. MPAG members noted that the differences in budget allocation and donor funding for malaria control between countries (e.g. Rwanda vs. South Sudan) may be an important underlying factor in the differences observed in mortality rates. It was suggested that these factors, as well as the underlying socioeconomic differences, could help to explain the differences in malaria outcomes in these countries. It was noted that reducing mortality means adopting a patient-centred approach by addressing the factors that lead to high mortality, including programmatic issues such as stockouts and treatment-seeking behaviours. MPAG also highlighted the need for better linkages between HBHI and the broader aims of UHC.

MPAG members were impressed by the report and congratulated Professor Evelyn Ansah and the committee on the detailed and informative evaluation of the HBHI approach that was carried out at the global level and in four of the HBHI countries: Cameroon, Ghana, Mali and Niger. MPAG members appreciated the key positive findings, including the engagement of key stakeholders at the national level, increased international attention and engagement, and better targeting of interventions and optimization of resources. However, MPAG members agreed with concerns raised in the report that, at country level, HBHI was viewed as a project rather than as an approach, and there was a lack of knowledge of and involvement in the HBHI approach at the subnational level. Although the HBHI response was affected by COVID-19, inadequate resources (including human resources) and unclear ownership and stewardship were identified as clear barriers to maximizing uptake. MPAG members discussed the need for clarity around SNT, and the need for strategies to address the introduction of new tools, such as vaccines, and their integration with the HBHI approach. One of the MVIP pilot countries, Ghana, has also been part of the HBHI programme. This experience can provide insights into the interaction between EPI and the national malaria programme as vaccine implementation is brought to scale. MPAG directed the Global Malaria Programme to consolidate the lessons learned and share these with countries and partners.

MPAG members discussed and agreed with the 10 recommendations of the report, noting the need for the addition of clear directives, action timelines and designated responsibilities for the recommendations. The discussion focused on recommendation 9 – the need for a functional monitoring and evaluation framework for the HBHI

approach. MPAG suggested that the development of the monitoring and evaluation framework could be part of the HBHI approach, with each country developing its own context-specific Theory of Change alongside a monitoring and evaluation framework. This would help to foster country ownership and identify appropriate stewardship strategies for the approach. MPAG members suggested that the Global Malaria Programme explore mechanisms to provide operational guidance that clearly defines the HBHI approach and how it can be adopted and adapted within high-burden countries.

Updates to the WHO guidelines for malaria: tafenoquine recommendation and G6PD diagnostics

Background

Based on the 2018 review of the Global Malaria Programme's process for developing WHO malaria recommendations, in November 2019, the Global Malaria Programme and the Department of Essential Medicines Health Products developed a "Master plan for developing recommendations on the use of tafenoquine and companion quantitative point-of-care G6PD in vitro diagnostics" (WHO internal document, 2019). The aim of the master plan was to coordinate activities as "one WHO" to develop recommendations on the use of tafenoquine and companion G6PD point-of-care tests as part of the WHO guidelines for malaria *(3)*; the WHO prequalification lists of finished pharmaceutical products *(8)* and in vitro diagnostics *(9)*; and the Model Lists of Essential Medicines *(10)* and Essential In Vitro Diagnostics *(11)*.

In line with these principles, the Global Malaria Programme will convene two GDG meetings. On 14–15 November 2023, the GDG on malaria chemotherapy will review the evidence and generate recommendations on tafenoquine and primaquine as anti-relapse therapy for *P. vivax* and *P. ovale*, and single low-dose primaquine to reduce the transmissibility of *P. falciparum*. On 30 November–1 December 2023, the GDG on malaria diagnostics will review the evidence and generate recommendations on near-patient diagnostic tests for G6PD deficiency.

WHO experts will review the evidence collated to respond to the following PICO (Population, Intervention, Comparator, Outcome) questions on 8-aminoquinoline medicines:

1. Is single-dose tafenoquine an alternative to standard-dose primaquine for preventing relapses in patients with G6PD activity > 70% who have received chloroquine therapy for acute *P. vivax* infection?

2. Is high total dose primaquine (7.0 mg/kg) more effective than low total dose primaquine (3.5 mg/kg) at preventing relapses to day 180 in patients with uncomplicated *P. vivax* malaria?

3. Does an intermediate (0.5 mg/kg) or high (1.0 mg/kg) daily dose of primaquine cause more gastrointestinal symptoms or adverse haemoglobin changes compared to a low (0.25 mg/kg) daily dose of primaquine?

4. Is it safe to administer primaquine to infants aged < 6 months and women breastfeeding infants aged < 6 months to reduce transmission and to prevent relapses?

5. In elimination settings, as well as in areas threatened by artemisinin resistance, a single low dose of primaquine of 0.25 mg/kg should be given with an artemisinin-based combination therapy (ACT) to patients with *P. falciparum* malaria.

WHO experts on near-patient G6PD tests will review the evidence collated to respond to the following PIRT (Population, Index Text, Reference Test, Target Condition) question: In patients undergoing G6PD activity testing, how accurate are near-patient tests for G6PD deficiency compared to quantitative spectrophotometric G6PD testing at the thresholds critical to inform administration of 8-aminoquinolines to prevent relapses of *P. vivax* and *P. ovale*? The critical thresholds relevant to the safe administration of tafenoquine and primaquine anti-relapse therapy will be < 30%, 30–70%, and > 70% G6PD activity.

Following the elaboration of the new guidelines for malaria sections, the inputs from the external review group and the submission to the WHO Guidelines Review Committee, the new recommendations on the use of tafenoquine, primaquine and near-patient G6PD tests will be published in April 2024, if both tafenoquine and near-patient G6PD tests are included in the relevant WHO prequalification lists.

MPAG conclusions

MPAG appreciated the Global Malaria Programme's efforts to review and provide evidence-based guidelines for treatment and anti-relapse therapy for *P. vivax*. The presentation was clear, and this issue is crucial for countries with *P. vivax* malaria and for elimination settings. There is an urgent need to finalize recommendations for the use of tafenoquine for anti-relapse treatment of *P. vivax*. This includes Prequalification approval of a suitable G6PD test and the associated guidelines for use. Tafenoquine was approved by the United States Food and Drug Administration over four years ago, but the guideline recommendation by WHO has been delayed by the lack of a point-of-care G6PD diagnostic test. A clear lesson to be learned is that planning at the earliest stages of product development for all ancillary requirements will serve to move products into use more rapidly to address unmet medical needs. MPAG noted that this was the only session dedicated to issues primarily impacting *P. vivax* and asked that in subsequent MPAG meetings more attention be given to this topic.

MPAG noted that the GDG on malaria chemotherapy will develop guidelines, considering evidence on various aspects. MPAG suggested that efficacy/effectiveness, tolerability, compliance, feasibility in remote areas and cost be considered by the GDG. MPAG members expressed concern about G6PD tests specifically for remote areas and requested that the GDG on diagnostics pay attention to this issue.

MPAG noted that it would be appropriate to review additional evidence on primaquine dosing, as new reports have emerged regarding the effectiveness of some of the currently recommended dosing regimens. However, MPAG members noted that if new recommendations differ from the current recommendations, this should be clearly communicated to countries and other stakeholders to avoid confusion. This is important in situations in which a current recommendation is proven to be less effective based on new evidence.

In response to questions from MPAG members, the Global Malaria Programme clarified that the primary focus of the GDG on chemotherapy will be to review the use of tafenoquine as anti-relapse treatment for *P. vivax*. The review on primaquine will include its use as an anti-relapse treatment for *P. vivax* in higher doses, as well as its role as a gametocide for *P. falciparum*; it is already being used in this way in some countries in the Americas. At this time, the role of tafenoquine as a gametocide for *P. falciparum* will not be considered.

Update on antimalarial drug resistance in Africa

Background

The *Strategy to respond to antimalarial drug resistance in Africa (5)* was launched in November 2022, following an extensive process that included an MPAG review. A review of data was done as part of the development of the strategy, and, at the time, artemisinin partial resistance had been identified in three countries in Africa. The review

also found that, while there were scattered reports of high treatment failure rates, there was no confirmed resistance to the partner drugs in the ACT.

K13 mutations associated with delayed clearance after treatment with an artemisinin-containing treatment are emerging and spreading in the Horn of Africa and East Africa. In the Horn of Africa, the mutation 622I has been detected in several countries, including Eritrea, Ethiopia, Somalia and the Sudan. The 622I mutation has been detected in parasites with histidine-rich protein (HRP) 2/3 deletions, which makes it difficult to detect these strains with regular HRP2-based rapid diagnostic tests. In Uganda, different K13 mutations appear to be spreading, and there are foci where validated markers of artemisinin partial resistance have been found in the majority of the parasites sampled. In Rwanda, the K13 mutation 561H is spreading though a different mutation, the 675V, is more common in western Rwanda. The mutation 561H has also been identified in the United Republic of Tanzania, primarily in Kagera close to the border with Rwanda. Based on evidence of the prevalence (> 5%) of a validated marker of artemisinin partial resistance and delayed clearance, artemisinin partial resistance has now been confirmed in four countries in Africa: Eritrea, Rwanda, Uganda and the United Republic of Tanzania.

Since the review of data on antimalarial drug efficacy and resistance done as part of the development of the *Strategy to respond to antimalarial drug resistance in Africa,* the results of two studies of artemether-lumefantrine (AL) in Uganda and the United Republic of Tanzania have indicated the potential low efficacy of this ACT. In Uganda, studies in 2022–2023 showed around 18% treatment failure after treatment with AL in two sites. Research in Uganda has also reported decreased sensitivity to lumefantrine in vitro. WHO is working with researchers and the country to support data validation to help facilitate action. In the United Republic of Tanzania, a study done in 2022 reported 10.1% treatment failure after treatment with AL in one site (Pwani).

As part of the operationalization of the strategy, WHO is convening two meetings in Kampala in November 2023: a regional stakeholder meeting on 7–8 November, which aims for alignment on intervention priorities to support countries responding to resistance, and a meeting on 9–10 November on the surveillance of drug efficacy and resistance for countries in East Africa and the Horn of Africa. To help prioritize interventions in the local context, the strategy proposes country assessments, looking at factors that could drive resistance in a given context, and the systems in place and the data available. This assessment will inform country-specific strategies and plans to respond to resistance. WHO is currently supporting an assessment in Rwanda. The aim of this work is both to develop a specific assessment and plans for Rwanda, and to guide future assessment methodology that can be used by other countries. A virtual consultation on expansion of the External Quality Assessment scheme to include molecular markers of antimalarial drug resistance was organized in July 2023. There was wide support for expanding the existing External Quality Assessment scheme to include drug resistance markers and molecular correction method. K13 markers were deemed the most important markers to include in the panels from the start.

MPAG conclusions

MPAG commended the Global Malaria Programme's substantial efforts to identify artemisinin partial resistance and ACT any lower-than-expected efficacy and coordinate the African regional response. MPAG considers this to be an urgent issue that poses a major threat to malaria treatment and control efforts across Africa. There are abundant data now showing that artemisinin partial resistance is spreading rapidly across East and East-Central Africa. There is a significant risk that, as previously occurred in the Greater Mekong subregion, resistance to ACT partner drugs will emerge, leading to significant ACT treatment failures. Widespread ACT treatment failures in Africa would have devastating consequences and it is essential to respond quickly.

MPAG strongly recommended that the level of urgency be raised. The emphasis needs to be on how to accelerate malaria elimination efforts in countries with artemisinin partial resistance, using existing tools. There needs to be prompt consideration of implementing treatment policy changes across the region, to move away from the

almost exclusive reliance on AL. Existing alternatives include ACTs such as artesunate-amodiaquine (where not already implemented), dihydroartemisinin-piperaquine, artesunate-pyronaridine and artesunate-mefloquine, either as primary ACTs or as part of a strategy of deploying multiple first-line therapies. Triple ACTs, which have proven to be effective in trials in the Greater Mekong subregion, could be considered, but only after inclusion in treatment guidelines. The addition of single low-dose primaquine to reduce the spread of artemisinin partial resistance is one of the key possible strategic responses. Support for the accelerated development of non-artemisinin-based combination therapies, currently in Phase 3 clinical trials, is also essential, although it is recognized that their implementation is several years away.

MPAG members' call for an immediate plan of action was strongly supported by the representatives from the President's Malaria Initiative, the Global Fund, and the Bill & Melinda Gates Foundation. The speakers emphasized the need to implement a coordinated regional plan. MPAG strongly appreciated this support and highlighted the critical need for resources to be committed to the Global Malaria Programme to implement recommendations.

The urgency of this topic was highlighted at the recent annual meeting of the American Society of Tropical Medicine and Hygiene (Chicago, United States of America, October 2023) and the Malaria Genomics Convening in Dakar in October 2023. Discussions on artemisinin partial resistance and the regional response will be held at the upcoming meetings in Kampala in November 2023, organized by the Global Malaria Programme. Based on the outcomes of the upcoming meetings, further activities, including additional convenings and implementation of coordinated activities to respond to resistance, may need to planned. These activities will require additional resources for completion in a timely manner.

There is also a critical need for more data from the surveillance network across Africa to help map gaps in knowledge and needs. In accordance with WHO's role in establishing norms and standards, it will be important for the Global Malaria Programme to validate reports of artemisinin partial resistance and therapeutic efficacy through established protocols. MPAG supports the expansion and harmonization of regional drug resistance surveillance networks, including the exchange of data in real-time to facilitate rapid and appropriate responses. Furthermore, MPAG supports the inclusion of molecular markers for artemisinin partial resistance in the standard panel of markers analysed by WHO collaborating laboratories.

MPAG also emphasized the need for more data on the impact of artemisinin partial resistance on the treatment of severe malaria with intravenous artesunate, so that decisions on therapeutic options can be made if treatment efficacy is compromised.

Update on the Mekong Malaria Elimination programme

Background

Over the past 10 years, the countries in the Greater Mekong subregion have made remarkable progress towards their collective goals of eliminating *P. falciparum* by 2023 and eliminating all human malaria species by 2030. Between 2013 and 2022, there was a 67% reduction in cases overall. *P. falciparum* and mixed cases declined by 92% and deaths due to malaria decreased by 95% over the same period. However, the continued unstable political situation in Myanmar has caused an overall increase in cases across the Greater Mekong subregion. Although most of the increased burden has occurred in Myanmar, the border regions of neighbouring countries, in particular Thailand, have also been affected. Reaching the unreached populations, particularly in remote and marginalized communities, is vital for malaria elimination. This requires a comprehensive, tailored and participatory approach that considers social, economic and political factors. The role of community-based volunteer health workers is especially important in gaining trust and understanding needs. Despite the presence of artemisinin partial resistance in the Greater Mekong subregion, several ACTs remain highly effective

against *P. falciparum*. *P. vivax* is the dominant parasite in the region, causing 83% of cases in 2022 and presenting a significant barrier to malaria elimination. Countries in the Greater Mekong subregion are preparing for national malaria-free certification, with subnational verification serving as a valuable programmatic exercise to support compliance with WHO processes and documentation. Planning for prevention of re-establishment of malaria is essential to fulfil the criteria for certification of malaria-free status.

MPAG conclusions

MPAG thanked the Global Malaria Programme and the Mekong Malaria Elimination programme team for providing an excellent and comprehensive summary that shows promising progress towards malaria elimination in the Greater Mekong subregion, while noting some evidence of potential setbacks. The situation in Myanmar is a major challenge to elimination that is difficult to control because of local political instability. Another challenge is that the other Greater Mekong subregion countries require continuous political and financial support from their own governments for malaria elimination and need technical support, especially for hard-to-reach communities and cross-border regions of malaria transmission. MPAG recommended that the WHO Regional Office for South-East Asia and Regional Office for the Western Pacific work with Chinese authorities, who can share the lessons learned from their successful within-country malaria elimination campaign. MPAG noted the very encouraging finding that artesunate-mefloquine is maintaining its efficacy in Cambodia five years after this ACT was introduced to replace dihydroartemisinin-piperaquine, which had succumbed to multidrug resistance. MPAG was encouraged by recent progress in reducing malaria cases and deaths in the Greater Mekong subregion. MPAG strongly supported the Mekong Malaria Elimination programme's increased emphasis on radical cure coverage to eliminate the *P. vivax* liver stage reservoir and its work with local teams to eliminate malaria.

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All documentation related to this meeting can be found at: https://www.who.int/news-room/events/detail/2023/10/30/default-calendar/24th-meeting-of-the-malaria-policy-advisory-group

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