

WHO Malaria Policy Advisory Group (MPAG) meeting

MARCH 2022

MEETING REPORT

SUMMARY

On 23–24 March 2022, the World Health Organization (WHO) Malaria Policy Advisory Group (MPAG) convened virtually to review updates and progress, and to provide guidance on thematic areas of work by the Global Malaria Programme.

The virtual meeting focused on eight topics in three open sessions: 1) an update on the RTS,S malaria vaccine and the draft framework for vaccine allocation; 2) the operational manual for subnational tailoring of malaria interventions; 3) *Plasmodium knowlesi* disease burden and transmission: implications for WHO certification of malaria elimination; 4) the report of the technical consultation to review the classification of glucose-6-phosphate dehydrogenase (G6PD); 5) an update on the WHO Guidelines for malaria; 6) an update on “Rethinking Malaria” and preparations for the Africa regional meeting; 7) an update on the framework for response to malaria in urban areas; and 8) an update on the development of a strategy to respond to antimalarial drug resistance in Africa.

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

- **RTS,S and the framework for vaccine allocation:** MPAG congratulated the Secretariat and its partners on quickly undertaking the consultative process to develop this framework. The principles and values underlying the draft framework were widely agreed upon and a number of specific issues were raised for consideration in finalizing and implementing the framework. MPAG also emphasized the need for careful monitoring and regular review of the framework implementation at a global level and within countries.
- **Operational manual for subnational tailoring of malaria interventions:** MPAG commended the Global Malaria Programme for the excellent preparatory work and presentation. They also endorsed the suggestion

to integrate this plan into the broader framework of health sector planning. Given that the document is not finalized, suggested areas of emphasis were provided by MPAG.

- **P. knowlesi:** MPAG thanked the Malaria Elimination Certification Panel (MECP) and the Global Malaria Programme for their work and careful consideration of this issue. MPAG acknowledged that this is a complex issue and one that presents unique challenges as countries near elimination. MPAG agreed that the concept of negligible risk suggested by the MECP may be the most practical way forward given the current situation. The assessment of the risk, which should include careful epidemiological and other investigations, should be conducted on a case-by-case basis.
- **Classification of G6PD:** MPAG acknowledged the importance of considering an updated classification of G6PD variants, noting that the latest update was in 1985 and that many more variants have since been described. The work by the Global Malaria Programme and panel of advisors was appreciated, and MPAG endorsed proceeding with this revised classification, including an explanation of the column labelled “haemolysis”.
- **WHO Guidelines for malaria:** MPAG members acknowledged the huge efforts exerted by the technical teams who prepared the WHO Guidelines for malaria. They complimented the strong, evidence-based process that the Global Malaria Programme has adopted to develop recommendations, and the consultative process to incorporate the opinions and contributions of a wider spectrum of malaria stakeholders and partners. The Group also acknowledged the work to make recommendations less prescriptive and the approach to support countries to use local evidence to adapt malaria control strategies.
- **“Rethinking Malaria”:** MPAG congratulated the Global Malaria Programme and its collaborators on the progress made so far in the global effort to rethink malaria. MPAG particularly appreciated the emphasis on those who are most affected by the disease playing a more central role in finding appropriate solutions to the malaria problem and agreed with the importance of viewing malaria as a societal problem, not purely a medical one, and of listening to the community.
- **Response to malaria in urban areas:** MPAG congratulated the Secretariat and the contributors to such an extensive consultation process. The framework was well received by the Group with some areas to consider for the finalization of the framework.
- **Strategy to respond to antimalarial drug resistance in Africa:** MPAG appreciated the considerable work already put into place to coordinate a structured, multidisciplinary plan with multiple workstreams to examine partial artemisinin resistance and the associated impact. MPAG also appreciated the importance of communicating this clearly without creating a sense of panic. The time to act is now, and MPAG fully supports the work of WHO and its partners in prioritizing this effort.

BACKGROUND

The World Health Organization (WHO) Global Malaria Programme convened the Malaria Policy Advisory Group (MPAG) for its 21st meeting via a virtual platform on 22–23 March 2022. 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, 19 MPAG members, national malaria programme (NMP) managers, the WHO Secretariat, and over 430 active observers discussed updates and progress in the work areas presented. The Group discussed conclusions and recommendations to the Global Malaria Programme in a closed session on day two.

The meeting participants were reminded of the procedures governing WHO's assessment of MPAG members' Declarations of Interest. 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. Fourteen members reported interests, which were posted on the meeting website in advance of the meeting. No MPAG members reported specific interests related to the agenda topics for decision. It was assessed that all members could fully participate in all sessions.

UPDATES FROM THE GLOBAL MALARIA PROGRAMME

The Director's report reflected on the Programmes's work since October, including highlights from the *World malaria report 2021 (1)* and its seven key messages:

1. During the COVID-19 pandemic, malaria-endemic countries succeeded in averting the worst-case scenario of malaria deaths projected by WHO by mounting an urgent and strenuous response. Still, moderate disruptions in the delivery of malaria services contributed to the considerable increases seen in malaria cases (14 million) and deaths (69 000) between 2019 and 2020.
2. The *World malaria report 2021* applied a new statistical method to calculate the number of malaria deaths among children under 5 years of age since 2000. This new methodology is being used across WHO and provides more precise cause-of-death estimates for young children for all diseases, including malaria.
3. Even before the emergence of COVID-19, global gains against malaria were levelling off and the world was not on track to reach the 2020 milestones of WHO's global malaria strategy. To reinvigorate progress, WHO and partners catalysed a new, country-driven approach to malaria control in high-burden countries that was beginning to gain momentum when COVID-19 struck.
4. On a global scale, progress against malaria remains uneven. Many countries with a low burden of the disease are moving steadily towards the goal of malaria elimination. In 2021, WHO certified two countries – El Salvador and China – as malaria-free. However, most countries with a high burden of the disease have suffered setbacks and are losing ground.
5. Over the past two decades, global progress against malaria was achieved, in large part through the massive scale-up and use of WHO-recommended malaria tools for the prevention, detection and treatment of the disease. The most recent data demonstrate these gains, while also highlighting the significant and sometimes widening gaps in access to lifesaving tools for people at risk of malaria.

6. The situation remains precarious, especially in sub-Saharan Africa, where the malaria burden remains unacceptably high, and a convergence of threats poses an added challenge to disease control efforts. At the same time, the COVID-19 pandemic is not over, and the pace of economic recovery is uncertain. Without immediate and accelerated action, key 2030 targets of the WHO *Global technical strategy for malaria 2016–2030* (2) will be missed and additional ground may be lost.
7. In 2021, WHO updated its global malaria strategy to reflect lessons learned over the past five years. Meeting the strategy's goals, including a 90% reduction in global malaria incidence and mortality rates by 2030, will require new approaches and greatly intensified efforts aided by new tools and better implementation of existing ones. Stepped-up investment is also essential.

The Director went on to highlight updates on normative work, including publication of the information note on the use of rectal artesunate following the decision from the October MPAG meeting; the malaria vaccine recommendation in the WHO Guidelines; and four new standard operating procedures (SOPs) to monitor insecticide resistance in mosquito vectors. Key meetings held this year include a meeting to develop target product profiles for glucose-6-phosphate dehydrogenase (G6PD) testing, the Malaria Vaccine Advisory Committee meeting, a technical consultation on the malaria rebound phenomenon and the 16th meeting of the Vector Control Advisory Group.

Finally, the report took a look back at some of the key achievements of the Department during the tenure of the Director. The *Global technical strategy for malaria 2016–2030* was endorsed by the Sixty-eighth World Health Assembly in 2015 and updated in 2021. With some revisions, the principles remain relevant, particularly ensuring country ownership and leadership. However, the challenge remains, as reductions in cases and deaths are off track by 40% and 42%, respectively. The process to reform the development of malaria recommendations started with a review in 2018, which identified three pain points: perceived lengthy process, inconsistent recommendations, and suboptimal use of the recommendations at country level. Since then, six technical areas have initiated evidence reviews, leading to new and updated recommendations that will continue to be incorporated into the consolidated *WHO Guidelines for malaria* (3). Two key country-facing initiatives were launched: 1) The E-2020 initiative was launched in 2017 to support 21 malaria-eliminating countries to achieve the 2020 elimination milestone. This initiative was followed by the E-2025, which was launched in 2021 to support 26 countries to reach the 2025 milestone. 2) The "High burden to high impact" (HBHI) approach was launched in 2018 to support the 11 countries with the highest burden of malaria. The Strategic Advisory Group on Malaria Eradication conducted a three-year study and published its conclusions in a report entitled *Malaria eradication: benefits, future scenarios & feasibility* (4). Nine countries have been certified as malaria-free since 2015: Maldives, Sri Lanka, Kyrgyzstan, Paraguay, Uzbekistan, Argentina, Algeria, El Salvador and China. In response to the challenges to malaria posed by the COVID-19 pandemic, malaria partners came together under WHO's leadership in seven cross-partner workstreams on: clinical trials with antimalarials and product development, surveillance and clinical epidemiology, supplies and commodities, malaria response and guidance, communications, coordination, and resource mobilization. Together, the worst-case scenario projected was largely averted. Finally, tackling drug-resistant malaria in the Greater Mekong Subregion (GMS) has been very successful, with investments from multiple partners and support from WHO leading to a dramatic reduction in cases from an estimated 650 000 in 2012 to 82 000 cases in 2020.

Looking forward, the Director emphasized the need to make progress on the African continent where the majority of malaria deaths occur. Biological threats will remain a challenge to malaria efforts, highlighting why continued investment in research

and development (R&D) is a priority. In order to make progress, malaria programme implementation must take a smarter data-driven public health approach, facilitated by less prescriptive recommendations to enable countries to adopt subnational approaches. Ensuring universal health coverage and addressing inequities in access to malaria interventions are becoming increasingly important so that hard-to-reach and vulnerable populations are not left behind. Finally, country ownership is critically important to enable data-driven approaches; donors and partners must align with national strategic plans.

The Director closed his report with a quote from the Malaria Commission (5) (1927): “The history of special antimalarial campaigns is chiefly a record of exaggerated expectations followed sooner or later by disappointment and abandonment of the work. This record of failure and disappointed hopes makes it clear that the only prospect of real progress lies in renewed activity in the continuous study of the disease in all its aspects...”

SUMMARY OF THE MPAG SESSIONS

Update on the RTS,S malaria vaccine and the draft framework for allocation of limited vaccine supply

Background: In October 2021, WHO issued a recommendation for the first malaria vaccine to be used for the prevention of *Plasmodium falciparum* malaria in children living in sub-Saharan Africa and in other regions with moderate to high transmission (6). It is projected that – at scale – using this vaccine as part of an integrated malaria control programme could save tens of thousands of young lives each year.

Current estimates suggest that the initial supply of the vaccine is insufficient to meet the needs of over 25 million children born each year in regions with moderate to high malaria transmission. It is an ethical imperative to address the underlying causes of the current scarcity and to pursue ways to accelerate increased supply to meet demand as soon as possible.

In parallel, until vaccine supply is sufficient to meet the need, a fair and equitable mechanism is needed to guide, in full transparency, how supply is prioritized, based on the best available evidence, shared values and appropriate input from key parties. As recommended by the Joint Strategic Advisory Group of Experts on Immunization (SAGE) and MPAG working group, the Secretariat has developed a draft Framework for the allocation of limited malaria vaccine supply and shared the working document with MPAG for guidance. This draft framework for the allocation of limited malaria vaccine supply outlines the proposed values, allocation principles, governance principles and key considerations for implementation. The framework aims to offer guidance globally on the allocation to countries of RTS,S/AS01 and other malaria vaccines as they become available, and guidance on prioritization of areas for vaccination within countries until supply constraints can be resolved. The intended audience for the framework includes global and national decision-makers involved in making allocation and prioritization decisions about malaria vaccines, including policy-makers in malaria-endemic countries, the manufacturer(s), Gavi, the Vaccine Alliance, and other funding, implementing and technical partners.

The governance principles of transparency, inclusiveness and participation, and accountability are proposed to guide the process for how this framework is developed

and how the resulting decisions are made and monitored. In addition, there are three proposed priority allocation principles and a tie-breaker allocation principle:

1. The first priority aim is to allocate the malaria vaccine to populations at greatest need, where the disease burden is highest and the risk of progression to severe disease or death is also highest.
2. The second priority aim is to allocate the malaria vaccine to countries for use in areas where the expected health impact is greatest, that is, where most lives can be saved with the limited available doses.
3. The third priority aim is to allocate the malaria vaccine to countries that commit to fairness and addressing the needs of marginalized individuals and communities in their malaria vaccination programmes.
4. The tie-breaker allocation principle of reciprocity applied to the RTS,S/AS01 vaccine would justify the allocation of vaccines to individuals or groups to whom something is owed because of burdens or risks they have assumed in helping to research and develop this vaccine.

A key implication of the proposed allocation principles is that countries will have to consider a phased vaccine roll-out, starting at the subnational level in areas with the greatest need – unless they prefer to wait until supply is available to cover all medium to high transmission areas at once.

Four key considerations of the draft framework include the following:

- Honour commitments to pilot countries to sustain vaccination for continued implementation in pilot areas (including expansion to comparator areas).
- Avoid or minimize the risk of suboptimal vaccine use and wastage.
- Ensure continuity and sustainability of access to the vaccine once a programme has started.
- Vaccine allocation should not perpetuate pre-existing structural injustices.

This framework is intended to be dynamic to support prioritization decisions over the coming years as supply ramps up. Periodic reviews and updates will ensure that it remains useful and appropriate.

MPAG conclusions: MPAG congratulated the Secretariat and its partners on quickly undertaking the consultative process to develop this framework. Members expressed concern over the severe discrepancy between the need and projected available vaccine supply. The Group supports the plan for finalizing and sharing the framework in the coming month. Although the principles and values underlying the draft framework were widely agreed upon, members emphasized the need for careful monitoring and regular review of the framework implementation at a global level and within countries. Many raised the importance of addressing health systems weaknesses. In addition, several observed that countries with poor data might find it difficult to identify areas of greatest need based on the proposed proxy measures and should receive appropriate support so as to not be disadvantaged as a result.

A number of specific issues were raised for consideration in finalizing and implementing the framework. It will be important to recognize the risk of disadvantaging countries with large populations that meet the high priority parameters through the application of

caps. The framework should be clear on how the reciprocity and solidarity commitment to countries that participated in developing the evidence for RTS,S will be applied when some countries fall outside the first two or three tiers of the proposed priority measures. One observer raised the issue of considering setting aside some allocation for humanitarian settings or displaced populations who may be missed by national processes and could be better served by non-state actors. Allocation might also prioritize doses for implementation research that may impact demand and need, including research on the optimal delivery strategy of RTS,S when provided in areas where seasonal malaria chemoprevention (SMC) is also implemented, and exploring the effectiveness of three versus four doses and fractional doses. Key considerations include that an efficient health service is required at all levels, in particular primary health care (PHC), for optimal vaccine uptake and coverage. Consideration should be given to the sustainability of access and to overcoming structural injustices.

Operational manual for subnational tailoring of malaria interventions

Background: National malaria strategic plans should be nested within the broader national health sector planning to relate to the most important health needs and demands of citizens; to ensure that programmes and interventions are evidence-based, cost-effective and fairly distributed, addressing the health needs of all population groups, particularly the most vulnerable; to inform national strategies and resource allocation; and to provide key reference information and evidence for policy-making, and monitoring and evaluation (M&E). The subnational tailoring of guidance on malaria interventions is anchored in the principles of value-based health services (VBHS) delivery. This approach takes into account economy, efficiency, effectiveness, equity and cost-effectiveness, but based on an understanding of what patients and communities value the most. The guidance is also anchored in the Paris Declaration and the Accra Agenda for Action calling out the need to respect country ownership and leadership in setting their own strategies for donors to align behind. These agreements emphasize inclusive partnerships, delivery of results, better coordination and efficiency, and mutual accountability. The operation manual covers the subnational tailoring of malaria interventions across the transmission continuum and builds on the HBHI approach.

The target audience consists of NMPs and their implementation partners; subnational entities responsible for coordination of implementation activities and engagement with communities on setting health priorities; technical experts supporting countries in the subnational tailoring of interventions; and funders. The manual is structured in five parts: 1) principles of and metrics for subnational tailoring of malaria interventions; 2) WHO-recommended malaria interventions and strategies: practical applications; 3) understanding baseline and current transmission levels and their determinants; 4) defining optimal intervention mixes; and 5) prioritizing interventions within a budget.

Part one outlines key principles and key questions, and defines key terms including subnational tailoring of malaria interventions, stratification, optimization and prioritization. Key metrics are identified related to environmental covariates, entomological measures, infection prevalence, cases, under-5 mortality, demographics and foundational metrics. Part two looks at the current WHO-recommended malaria interventions considering the level of personal protection, the impact on transmission, and longevity and durability of effectiveness. A more detailed look considers practical applications such as impact end-points, considerations for scale-up, geographical targeting and prioritization for impact within a budget.

Part three of the manual covers the baseline and current transmission levels and their determinants. A baseline in its strictest sense refers to the level of transmission where

there are no interventions, including the provision of any effective treatment. Given the possibility of changes in the baseline unrelated to control measures, at least in settings where health systems are sufficiently robust that some access to effective treatment is always likely to be present, it may be most practical to use the last measurement prior to the implementation of major preventive interventions (e.g. vector control or chemoprevention). Part four describes defining the optimal mix of interventions and strategies. Detailed data around the previous scale-up of interventions and other determinants within a unit area are key to understanding the likely incremental impact of any future malaria intervention and its interaction with other determinants. The amount an intervention reduces malaria from its baseline level is likely to differ greatly across operational units and will depend, for example, on the magnitude of the baseline itself, as well as the metric used to measure this baseline.

It will also depend on the fraction of the population covered by an intervention, the extent to which the intervention provides personal protection from infection or disease in those covered and the magnitude of the intervention's impact on transmission. As such, two places with very different baselines can have the same level of current risk due to variation in the effectiveness or coverage of interventions, and the effect of other determinants. The manual also outlines criteria for making decisions on intervention choices within a constrained budget. This process of prioritization is designed to ensure optimal impact for available resources, but taking into account factors such as equity and national political and policy contexts that also inform resource allocation. The final part describes how to monitor and measure the impact of intervention mixes.

The manual is expected to be finalized for internal and external review, including by NMPs, in April/May 2022. Dissemination along with training materials is anticipated by the third quarter of 2022.

MPAG conclusions: The Global Malaria Programme presented a summary of a framework currently under development, which will provide both general and detailed guidance to countries seeking to implement a stratified approach to malaria control. It was noted that strategic information on the malaria situation and its determinants is a key pillar of major WHO initiatives such as HBHI, but that the framework will be beneficial for the entire range of transmission settings including countries with low transmission and those in the high-burden categories. It was recognized that even in HBHI countries, there is sufficient in-country heterogeneity to warrant sub-nationally stratified interventions.

MPAG commended the Global Malaria Programme for the excellent preparatory work and presentation. They endorsed the suggestion to integrate this plan into the broader framework of health sector planning. Given that the document is not finalized, suggested areas of emphasis were provided by MPAG:

1. MPAG advised that the framework be simplified to ensure that national programmes at all levels can implement it. The manual should also suggest the type of human resource capabilities needed to implement the subnational tailoring of interventions.
2. Further clarification is needed on how demographic and temporal variations in malaria burden could be incorporated into the intervention packages designed for delivery on the basis of geographical strata.
3. It was noted that the subnational tailoring process takes into consideration other determinants beyond public health, but guidance should also focus on the agriculture, environment, housing and finance sectors. In some countries, there may be subnational zoning on an economic basis, with certain districts being agricultural or mining districts, for example. This zoning may influence malaria

risk and should be considered when designing subnational malaria strategies. Similarly, contributions from non-health sectors and from the private sector should be considered and clear mechanisms included for countries to consider.

4. While this framework will be important for control purposes, it may also be used to guide R&D, for example by identifying areas where key innovations are necessary. Examples include identifying the potential for SMC in localities where the transmission period is short enough to warrant it, and whether interventions such as monoclonal antibodies or new SMC treatments may be trialled for future consideration.
5. Further information is needed on how cost-effectiveness and other considerations should be incorporated when deciding to either combine or use individual interventions. For example, while in some cases it may be more impactful to combine two interventions, the logistics and resource basket may favour deployment of only one at high coverage.
6. There are several metrics listed, even though parasite prevalence is prioritized. One question from the audience was how vector surveillance and associated indicators will be considered in this framework.

***P. knowlesi* disease burden and transmission: implications for WHO certification of malaria elimination**

Background: During its 10th meeting on 3 March 2022, the Malaria Elimination Certification Panel (MECP) reviewed the available evidence on the disease profile, severity and fatality of *P. knowlesi* (7); a systematic literature review on the available evidence of whether human–mosquito–human transmission can occur (8); and an analysis of *P. knowlesi* case surveillance data from Malaysia. This information served as the background for a substantive discussion on the implications for WHO certification of malaria elimination.

WHO certification of malaria elimination is an international confirmation of a country's malaria-free status. Achieving certification requires proof that local malaria transmission by *Anopheles* mosquitoes has been fully interrupted, resulting in zero incidence of indigenous cases for at least the past three consecutive years, and the presence of an adequate surveillance and response system for preventing re-establishment of transmission that is fully functional throughout the country (9). Once certified, countries are entered into the Official Register, as instructed by the World Health Assembly Resolution WHA13.55 in 1960. The Official Register provides information to all concerned, including international travellers, on where the risk of malaria infection is zero or negligible. Since its establishment, 40 countries and territories have been added to the Register. Up until now, certification has been granted when countries have interrupted transmission of *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*, often termed "human malaria parasites". Admittedly, the term "human malaria parasite" is poorly defined and has at times been taken to mean "parasites that can infect humans" or more rarely "parasites that can be transmitted from humans to vectors and to humans again".

The MECP concluded that:

1. For countries where transmission of the four "human" *Plasmodium* species has been interrupted but *P. knowlesi* cases continue to occur, certification should depend on careful assessment of the risks. When countries are reporting hundreds or thousands of *P. knowlesi* cases, certification of malaria-free status should be postponed. An arbitrary low threshold might be applied, e.g. 10

or fewer cases per year, below which a country can be potentially certified as having eliminated malaria, as the risk of zoonotic transmission might be considered “negligible”.

2. The MECP calls on WHO and partners to support countries dealing with relatively high levels of *P. knowlesi* transmission to strengthen control based on appropriate multidisciplinary approaches.
3. Where *P. knowlesi* cases are being reported, countries should aim to further improve the health care system and strengthen case-based surveillance in affected areas. While field epidemiology remains relevant and important, genomic epidemiology is likely to play a role in surveillance and may eventually help to clarify issues related to transmission pathways, as well as the most effective forms of control.
4. All countries’ efforts to achieve malaria elimination should be encouraged, even if the burden is due to zoonotically transmitted malaria.

The MECP proposes the establishment of a joint working group involving WHO and the ministries of health of affected countries to better define the problem and develop more effective strategies to control the transmission of *P. knowlesi*.

MPAG conclusions: MPAG thanked the MECP and Global Malaria Programme for their work and careful consideration of this issue. MPAG acknowledged that this is a complex issue and one that presents unique challenges as countries near elimination and the impact that expanding the definition of elimination to include simian malarias might have on country efforts to eliminate malaria where simian malarias exist. It is well established that *P. knowlesi* is a zoonotic infection that can infect humans and lead to disease, including severe disease and death. Elimination of the parasite in the zoonotic host seems unlikely and therefore the MECP is suggesting setting criteria for negligible risk. There are several knowledge gaps that prevent the establishment of a universal and quantitative criterion for *P. knowlesi* transmission, including detailed knowledge of vector behaviour and vectorial capacity and the extent of human transmission chains. Additional suggestions came up during the discussion, but these were not aligned with the objective of certification, which is to assess the interruption of mosquito-borne transmission, and the purpose of the Official Register. In addition, MPAG acknowledged that while *P. knowlesi* is the most common cause of zoonotic infections, there are other simian malaria parasites that can infect humans, so this issue may arise in other elimination settings.

MPAG agreed that the concept of negligible risk suggested by the MECP may be the most practical way forward given the current situation. The assessment of the risk, which should include careful epidemiological and other investigations, should be conducted on a case-by-case basis and reviewed with MPAG before a decision is taken. MPAG recommended that additional research addressing the specific knowledge gaps be undertaken and that the Global Malaria Programme work with affected countries to develop strategies and interventions to reduce *P. knowlesi* transmission.

Report of the technical consultation to review the classification of G6PD

Background: G6PD deficiency is an X-linked genetic condition affecting an estimated 500 million people worldwide. It causes neonatal jaundice, acute haemolytic anaemia, and chronic non-spherocytic haemolytic anaemia (CNSHA). The acute haemolysis can be triggered by eating fava beans (“favism”), exposure to several medicines,

or infection. The occurrence of acute haemolytic anaemia after exposure to the 8-aminoquinolines tafenoquine and primaquine is an important concern, as these are the only available medicines that are effective against the hypnozoite stage of *P. vivax* and so they are needed for the elimination of this malaria parasite.

The first classification of G6PD-deficient variants was made in 1966 and updated by a WHO Working Group in 1985. This classification is still used today. Since 1985, the full cDNA sequence of the G6PD enzyme was published, enabling the full genetic characterization of variants. In the last 36 years, over 230 genetic variants were identified. Many studies reported a considerable overlap between Class II and Class III variant phenotypes, specifically in terms of the severity of haemolysis and neonatal jaundice, raising questions about the value of having separate classes.

The Global Malaria Programme convened a panel of temporary advisors in January 2022 to review the current classification and to recommend changes based on extensive reviews of genotype and phenotype associations. WHO commissioned a literature review to examine the variability of G6PD activity for variants currently in Classes II and III, and also invited the presentation of an interim analysis of an individual patient meta-analysis investigating the variability of G6PD activity among genetic variants. There was general consensus among the panelists that the variation in enzyme activity values for the same variant may reflect both technical and biological factors. The participants noted the shortage of reliable data (especially for some variants) and the need for more research on phenotypic/genotypic associations, using standardized methodologies and procedures across multiple populations to generate more reliable data on individual variants.

The panel concluded that:

- the variability of activity for most genetic variants across the arbitrary threshold of 10% that distinguishes between Class II and Class III variants presents a strong argument to abandon this separation in any future classification;
- Class I should be retained, as CNSHA is a rare chronic condition that is well characterized with specific clinical manifestations associated with G6PD deficiency;
- Class V was based on a single case reported in the literature but not confirmed by further studies and, therefore, does not need to be retained; and
- because of the variability of activity for any single variant, the new classification needs to include a range around the reported median enzyme activity.

The panel proposed a new classification scheme of G6PD variants based on the median residual enzyme activity expressed as a percentage of normal activity as follows:

PROPOSED WHO CLASSIFICATION OF G6PD GENETIC VARIANTS IN HOMOZYGOUS DEFICIENT FEMALES AND HEMIZYGOUS MALES		
Class	Median of G6PD activity	Haemolysis
A	< 20%	Chronic (CNSHA)
B	< 45%	Acute, triggered
C	60–150%	No haemolysis
U	Any	Uncertain clinical significance

Currently, no variants have been identified in homozygous deficient females or hemizygous males that have median G6PD enzyme activity falling between 45% and <60%. Therefore, a gap has been left between Classes B and C. If new variants are found with median G6PD enzyme activity in this range, these should be included in the "U" class and studied until solid evidence is found that they induce acute haemolytic anaemia (= Class B) or do not pose a haemolytic risk (= Class C). Based on new evidence, the thresholds may then need to be revisited. It should be emphasized that this system is for classifying genetic variants of G6PD according to their phenotypes and should not be used to classify individual patients with G6PD deficiency.

The panel recommended that WHO consider developing standard criteria to characterize the genotypes and phenotypes of G6PD variants to improve comparability across studies and to inform the classification of new and existing variants. Any new variant should be assigned a tentative percent activity value only if this has been measured at steady state using a validated quantitative reference test in at least three samples from unrelated males. Other items to be considered include the number of individuals required to examine the distribution of G6PD activity, the number of laboratory replica measurements, the criteria to define normal reference values, genetic relationships among cases, methodologies for measuring G6PD activity, phenotypic screening and variant identification, and the criteria for including or excluding subjects with concurrent infection or haemolysis. As variants were identified at the molecular level for which important functional properties are unknown, it is desirable to measure at least KmG6P and thermostability for these and any new variants. Future research should also aim at addressing important gaps in knowledge, namely the risk of severe haemolysis associated with known and potential triggers in already described variants and the identification of other biological factors that might influence haemolytic response (e.g. enzyme activity in reticulocytes).

MPAG conclusions: MPAG acknowledged the importance of considering an updated classification of G6PD variants, noting that the latest update was in 1985 and that many more variants have since been described. The work by the Global Malaria Programme and panel of advisors was appreciated, including the proposed revised classification based on two detailed literature reviews. MPAG endorsed proceeding with this revised classification. An important component of the new proposed classification is the merging of the former Classes II (severe) and III (moderate to mild), as considerable overlap in phenotypes (G6PD residual activity and clinical manifestations, namely haemolysis) was noted for certain variants. MPAG noted that the revised classification has the stated goal of classifying genetic variants based on the median G6PD activity; this is purely descriptive and not intended to be used to classify individual patients and their risk of haemolysis.

The accompanying description indicated in one place that the new classification "should be practical and relevant for clinical use". MPAG was of the view that this language needs to be revised so that the message is solely about defining a revised classification, whose information should not be misconstrued as a tool to help determine patient risk with drugs (such as primaquine or tafenoquine) that can trigger haemolysis. The revised classification needs to explain the column labelled "haemolysis".

Members were concerned about the wide range of functional G6PD enzyme activity seen with some variants, such that variable individual results may occur in a class different from the median value. Elements contributing to this variability could include non-standardized assays or the use of different spectrophotometric instrumentation, in addition to biological variability. MPAG also strongly supported the stated need for further research on how to better standardize the current sampling/testing protocols to reduce technical variability; this would not affect the revised classification, but would strengthen its value.

Update on the WHO Guidelines for malaria

Background: The pathway for developing guidelines is articulated in three phases: 1) better anticipate, 2) develop recommendations, and 3) optimize uptake with a feedback loop to enable continuous updates and improvement. The *WHO Guidelines for malaria* (3) were first published in February 2021, consolidating all of the recommendations for vector control and case management. Further updates were published in July 2021 on vector control and in February 2022 on the malaria vaccine; the next update is expected by the end of this month. The French translation of the Guidelines has been available since August 2021, and the Spanish and Arabic translations will be launched in the coming months. The Guidelines are available through the MAGICapp online platform (<https://app.magicapp.org/#/guideline/5701>), via a PDF on the Global Malaria Programme website, and through the malaria toolkit app (<https://www.who.int/teams/global-malaria-programme/malaria-toolkit-app>) for mobile devices.

Four Guideline Development Groups (GDGs) have been convened to support the review of evidence and formulation of recommendations on vector control, elimination, chemoprevention and treatment; an additional GDG on diagnosis will be convened this year. In addition, the malaria vaccine recommendation was developed through a joint process of MPAG and the Strategic Advisory Group of Experts on Immunization.

Key technical updates include the following:

- **Vector control** – There has been an update of the conditional recommendation for pyrethroid-PBO nets; no change to the conditional recommendation against co-deployment of IRS and ITNs; and for vector control in humanitarian emergencies – a new strong recommendation for ITNs and a new conditional recommendation for IRS. The third set of evidence reviews will consider topical repellents, residual surface treatments and new nets towards the end of the year.
- **Interventions for the final phase of elimination and prevention of re-establishment** – The recommendations on accelerator strategies, targeted strategies and reactive strategies have been concluded and submitted for approval. Overall, there was very low to low certainty of evidence and the GDG judged chemoprevention strategies more favourably than test and treat strategies. Mass drug administration and mass relapse prevention will appear in the chemoprevention section of the Guidelines. A malaria elimination orientation curriculum is nearing completion. It will be launched on the OpenWHO platform and be available for download.
- **Chemoprevention** – The new and updated chemoprevention recommendations include perennial malaria chemoprevention (PMC), formerly known as intermittent preventive treatment of malaria in infants, SMC, mass drug administration, intermittent preventive treatment in pregnant women (IPTp), chemoprevention in school children and post-discharge malaria chemoprevention (PDMC). The meetings have been concluded and the approval processes are underway.
- **Treatment** – Three topics are currently under review: artesunate-pyronaridine for the treatment of uncomplicated *P. falciparum* malaria; whether any artemisinin-based combination therapy (ACT) is as safe and efficacious as quinine-based therapies for uncomplicated malaria during the first trimester of pregnancy; and whether the currently recommended total dose of primaquine can be given safely and effectively over a shorter period than 14 days for radical cure of *P. vivax* and *P. ovale* malaria.

- **Diagnosis** – Recommendations concern the use of near-patient G6PD tests; the first GDG meeting to finalize the PICO questions is planned for May 2022.

The third area of work is to optimize uptake of WHO recommendations and guidance. The Global Malaria Programme has developed a dissemination strategy to improve the way that WHO's malaria guidance is packaged and shared, and is seeking input from national, regional and global stakeholders. Three key digital platforms provide the foundation for dissemination: the GMP website, the MAGICapp platform and the mobile app. Additionally, the Global Malaria Programme has started developing short animated videos that describe WHO malaria recommendations in a simple and visually engaging way. In February 2022, the Global Malaria Programme convened its first meeting of the WHO Malaria Dissemination Taskforce to provide inputs on the dissemination strategy; these inputs were then prioritized as short-term or longer term priorities.

MPAG conclusions: MPAG members acknowledged the huge efforts exerted by the technical teams who prepared the WHO Guidelines for malaria. They complemented the strong, evidence-based process that the Global Malaria Programme has adopted, and the consultative process followed to gauge the opinions and contributions of a wider spectrum of malaria stakeholders and partners.

The Group acknowledged the work to make recommendations less prescriptive and the approach to support countries to use local evidence to adapt malaria control strategies included in the Guidelines. MPAG agreed that it is important to share information about when the updates will be disseminated, so that national programmes and stakeholders can anticipate adaptation and adoption of relevant recommendations in their settings. MPAG appreciated the establishment of a feedback loop from malaria control policy-makers and service providers – especially frontline workers of malaria health services and control intervention implementers. MPAG suggested making the research gaps identified during the evidence review process more visible, so that research addressing knowledge gaps can be undertaken and feed back into the recommendation development process.

MPAG asked if the Guidelines address any health system issues related to malaria service delivery or implementation of the control interventions that may negatively impact operationalization of the Guidelines at country level. Examples included supply management, laboratory equipment and logistics; MPAG suggested including references to specific WHO documents that address relevant health system issues for each chapter of the updated Guidelines.

Update on “Rethinking Malaria” and preparations for the Africa regional meeting

Background: “Rethinking Malaria” is an urgent response to the malaria crisis, which predominantly impacts the African continent. The focus has moved from a discussion on what needs to change to how to make change happen. The initiative acknowledges the current global context and the specific African context. Key considerations from the Harvard-led rethinking include understanding the perception of the problem – that malaria needs to be viewed as a societal problem, not as a medical problem alone, and that malaria eradication needs to be led by endemic countries in partnership with multiple stakeholders. Investing in and empowering the health workforce through readiness, training and education of health workers at all levels is critical, as is the visibility and use of reliable and timely data. Globally, greater attention to innovation

and problem-solving for malaria elimination and support for endemic countries in entrepreneurship, R&D and manufacturing is needed.

African thought leaders have recognized that the scale of the Africa malaria challenge is underestimated, requiring a compelling narrative that inspires change and African-led and -owned solutions and innovations. The malaria response should be embedded within PHC, which is rooted in a commitment to social justice and equity. It is time to listen to frontline workers and communities, who understand the factors driving their continued experiences of malaria and are well placed to identify appropriate solutions consistent with the epidemiology and ecology of malaria transmission. Defeating malaria requires that its management be integrated into the delivery of quality services, and recognition that wider determinants of health can be addressed through a coordinated broader multisectoral approach. Reliable and timely data and information must be generated, analysed and used by all decision-makers, starting with where it is collected. Success will require learning from what is already working, including the HBHI approach. Strategic investments are needed to strengthen Africa's capacities and institutions.

This issue of governance is key. African country leadership is essential. An analysis of the regional political context will consider whether political declarations for malaria have been successful and identify opportunities to reignite African political commitment. The political leadership needs to be coupled with technical leadership at all levels and the engagement of communities. Partners play an enabling role by supporting the national-level dialogue on the national plan, aligning behind a fully costed multi-year business plan and annual operational plan, and supporting national M&E to inform planning.

Other areas of importance include: embedding the malaria response in PHC; the need to view malaria as a societal problem, not as a medical problem alone; and applying a multisectoral response. Defeating malaria requires integration into the delivery of quality services and the empowerment of frontline workers and communities to identify solutions appropriate for their context. Participatory approaches are needed to analyse who is missing out and the barriers they face to ensure equitable access to quality services. The wider determinants of health can be addressed through a coordinated broader multisectoral approach, but there is inadequate knowledge on how to incentivize the different sectors to play an effective role. There is a need to review where success has been possible to extrapolate that success to other settings and countries.

A malaria stakeholder meeting is planned for quarter three of 2022 as a policy-level consultation to discuss the future of the malaria control and elimination in Africa, based on the feedback from multiple streams of analysis. The four objectives are:

- to review the findings and conclusions of the "Interim assessment of HBHI lessons learned";
- to interrogate the findings and recommendations of the Rethinking Malaria in Africa: Conference of African Thought Leaders convened by the WHO Regional Office for Africa (AFRO); recommendations of "Rethinking Malaria in the context of COVID-19 global engagement" undertaken by Harvard University and its partners; and recommendations of the RBM meeting on multisectoral action against malaria, and distil implications and practical steps for action;
- to assess the findings of the analysis of the political context in Africa and identify actions needed to further establish political commitment; and

- to review experiences from the front line and outcomes of country case studies on enhancing community participation, and identify strategic opportunities for further integrating malaria within PHC in the context of the Declaration of Astana (10).

MPAG conclusions: MPAG congratulated the Global Malaria Programme and its collaborators on the progress made so far in the global effort to rethink malaria. MPAG appreciated the emphasis on those who are most affected by the disease playing a more central role in finding appropriate solutions to the malaria problem. MPAG particularly agreed with the importance of viewing malaria as a societal problem, not a purely medical one, and of listening to the community. MPAG highlighted that the multisectoral approach proposed would be strengthened by a supportive legislative environment.

Members called out that this is not just a malaria crisis, but also a health system and equity crisis that requires an urgent and coordinated response. MPAG noted with satisfaction the efforts to engage stakeholders on the African continent to further deliberate on the issue and viewed this as a critical and important step in the process. It was noted that facilitating the involvement of African health policy and system experts would contribute to better understanding of how to strengthen the system for malaria control. MPAG further recommended that, in the proposed consultation, African stakeholders should seriously consider the issue of mobilizing domestic resources and improving efficiency in the context of limited resources.

MPAG members highlighted the importance of developing strategies in endemic countries for medium- to long-term promotion of local capacity-building at the different levels of decision-making to ensure sustainability of expertise and local policy decisions that are grounded in local input rather than in the views of ad hoc consultants. MPAG also highlighted the importance of a prioritized research agenda for malaria to guide R&D.

Update on the framework for response to malaria in urban areas

Background: By 2050, with the urban population more than doubling its current size, nearly seven out of 10 people will live in cities, with 90% of this growth occurring in Asia and Africa. This rapidly increasing urbanization has been recognized as a major developmental, social and health concern, leading to the 2016 launch of the United Nations' New Urban Agenda as part of the 2030 Agenda for Sustainable Development. Since 60% of the urban areas that will exist in 2050 have not yet been built (11), there is a unique opportunity to plan ahead and make cities resilient against the threat of these diseases.

Malaria is a wholly preventable and treatable disease, yet each year it kills over 600 000 people and makes over 200 million sick (1). Malaria transmission in urban areas is modified considerably by human activities, with benefits and risks. Well planned urbanization helps reduce malaria transmission through the destruction of mosquito breeding sites, improved housing, increased living standards, and expanded access to health care. However, urbanization in malaria-endemic countries comes with some risks, as large-scale rural to urban migration results in the expansion of unplanned settlements and increased socioeconomic inequity, especially in peri-urban areas and urban slums. These developments can lead to the adaptation of vectors to polluted waters (12). Furthermore, a large fraction of the population in urban areas seeks malaria treatment in the private sector, leading to very poor urban households incurring punitive health expenditures. A large number of malaria cases may also be due to

infections acquired outside the vicinity of the city or town, without major risks of onward transmission in the urban setting, requiring adaptation of preventive measures.

The Global response framework for urban malaria is designed to support the control and elimination of urban malaria to achieve the targets set in the *WHO Global technical strategy for malaria, 2016–2030* (2). The target audience of this framework includes city leaders and heads of national public health and malaria programmes, together with the main stakeholders in governance, policy-making and service delivery to people exposed to malaria living in urban areas. The vision is a world where towns and cities are free of malaria and other mosquito-transmitted diseases. The aim is to reduce the burden and threat from malaria through effective locally adapted, sustainable control measures.

MPAG conclusions: MPAG congratulated the Secretariat and the contributors of such an extensive consultation process. Overall, the framework was well received by the Group. MPAG had some suggested inputs for the finalization of the framework:

- It would be helpful to develop an M&E framework that further articulates the planning and tracking of the urban malaria activities.
- MPAG requested the inclusion of more recent examples of tools and/or case studies in urban areas.
- The importance of building implementation capacity must be stressed.
- The importance of mapping and adapting key data sources to ensure the magnitude of the problem is well characterized should be highlighted.
- MPAG recognizes the fundamental values of sanitation, clean water and adequate housing in addressing multiple public health problems in urban areas. Assessing these measures for their impact on vector control in urban settings is challenging and unlikely to meet the evidence-based standards for guideline development. Where feasible, the urban framework should be aligned with the core principle of using evidence-based interventions in guiding the selection of vector control measures.
- MPAG questioned the evidence for discounting the potential impact of ITNs and other measures in urban areas as these measures are the critical components in rural areas.
- The role of the education sector is very important and should be called out.
- Tension and fragmentation of health services are barriers to patients accessing malaria diagnosis and treatment. There are, however, successful examples of the involvement of the private sector in malaria prevention and control in urban areas.
- The framework should consider the increased risk of malaria in older age groups, including the risk of severe malaria.

Update on the development of a strategy to respond to antimalarial drug resistance in Africa

Background: ACTs were originally introduced more than 20 years ago to prevent the emergence of drug resistance that was already impacting decades-old monotherapies such as chloroquine. While there are currently six ACTs recommended in the *WHO*

Guidelines for malaria (3), artemether-lumefantrine (AL) is the most used, comprising over 85% of the antimalarial courses procured by the Global Fund.

While artesunate-amodiaquine (ASAQ) is widely used in francophone Africa, the remaining ACTs are rarely used, except perhaps in the GMS, where artemisinin (ART) partial resistance appeared 15 years ago. With the heavy use of AL, especially in African countries where the malaria burden is the greatest, ART partial resistance is emerging, as confirmed by a 2021 study in Uganda, Rwanda and other Eastern African countries. This is due to new mutations that have emerged in multiple foci and not from resistant parasites imported from the GMS – a hypothesis that had been raised by malaria experts. This growing phenomenon is only reinforced by the misuse or overuse of artemisinin-based therapies on the African continent, such as:

- the overuse of injectable artesunate by clinics in some countries for commercial reasons;
- the absence of referral following rectal artesunate pre-referral treatment (meaning that all the parasites might not be cleared); and
- the use of non-effective artemisia tea, which still contains enough artemisinin to contribute to the emergence of resistance.

While ACT treatments are still effective, studies suggest that they take longer to kill *P. falciparum* parasites. Early evidence also suggests that failures of partner drugs are emerging, notably lumefantrine (the partner drug in AL) and piperazine (the partner drug in DHA-piperazine), as put forward by the United States Centers for Disease Control and Prevention (to be confirmed, might be due to an analysis issue).

Emerging resistance, both to ART derivatives and partner drugs poses a major threat to the fight against malaria in countries that are far from being on the path to malaria elimination. Additional ACTs recommended by WHO – beyond AL and ASAQ – often face market failures, which means that rapid scale-up would be challenging with prices three to four times that of AL and a limited number of quality-assured suppliers. In parallel, new tools are unlikely to help solve this problem soon, with a weak pipeline of non-ACTs. More broadly, given that the antimalarial market is mature with low margins, malaria is not a priority disease for innovation by pharma companies.

There is a need to define a new drug resistance strategy to both better use existing tools to prevent the emergence of resistance and to develop new tools and strategies to tackle resistance once it has emerged. Learnings from the *Global plan for artemisinin resistance containment (GPARC)* (13) and the GMS elimination strategy (14) should be leveraged for this effort. The strategies that were successfully deployed in the GMS, for instance rapidly scaling up ACTs and promoting the use of single-dose primaquine, are, however, unlikely to be sufficient in non-elimination settings. The strategy for Africa will have to be comprehensive and cover areas beyond the immediate scope of drug resistance, for example by addressing counterfeit drugs, clarifying treatment guidelines, and using other tools such as vector control interventions, among other potential solutions.

MPAG conclusions: MPAG expressed concern about the evidence of ART partial resistance in *P. falciparum* parasites in Uganda, Rwanda and the Horn of Africa presented. This puts increased selective pressure on the partner drug, which could potentially increase the risk of resistance and ACT treatment failure. The need to define a strategy to actively monitor the emergence of ART partial resistance in Africa was emphasized. MPAG appreciated the considerable work already put into place to coordinate a structured, multidisciplinary plan with multiple workstreams to

examine ART partial resistance and the associated impact. MPAG also appreciated the importance of communicating this clearly without creating a sense of panic. MPAG feedback included incorporating an analysis of societal and behavioural contributions to the emergence of ART partial resistance, in addition to the focus on genetic and clinical aspects.

MPAG members highlighted the importance of this topic and the need to quickly assess the extent of ART partial resistance emerging and spreading in Africa. Incorporating this into an MPAG-supported declaration of the malaria crisis in Africa could help mobilize resources. This view is based on experience from the GMS where ART partial resistance was already highly prevalent in the parasite population years before the first clinical reports. MPAG was of the view that the time to act is now, and expressed full support for the work of WHO and its partners in prioritizing this effort.

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All documentation related to this meeting can be found at: <https://www.who.int/news-room/events/detail/2022/03/23/default-calendar/21st-meeting-of-the-malaria-policy-advisory-group>

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