

# WHO Malaria Policy Advisory Group (MPAG) meeting

OCTOBER 2022

MEETING REPORT

## SUMMARY

On 11–13 October 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 11 topics in five open sessions: 1) the “High burden to high impact” (HBHI) approach: progress, challenges, lessons learned and way forward; 2) the role of comparative assessment in the WHO evaluation of vector control products using non-inferiority analysis for products of the same class; 3) an update on the *WHO Guidelines for malaria*; 4) optimizing the uptake of WHO guidance on malaria and the work of the Dissemination Taskforce; 5) feedback on the uptake of chemoprevention recommendations; 6) an update on the RTS,S malaria vaccine roll-out; 7) an update on malaria elimination and the technical consultation on prevention of re-establishment of malaria; 8) an update on the *Global framework for the response to malaria in urban areas*; 9) an update on rectal artesunate for pre-referral treatment of severe malaria – independent review of evidence and field manual; 10) an update on *Plasmodium falciparum* histidine-rich protein 2 and 3 (*pfhrp2/3*) gene deletion issues; and 11) an update on the spread of *Anopheles stephensi* in Africa and the WHO response.

The key conclusions of MPAG to the Global Malaria Programme included the following.

- **HBHI approach:** MPAG members noted the progress and challenges faced by the approach and commended WHO, national authorities and malaria programmes, and partners for persevering in the face of the pandemic and related supply-chain disruptions. Members were concerned to learn that malaria-specific investments from national governments and some bilateral partners were static or in decline and recommended that outputs from the “rethinking malaria” exercise be
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revisited to guide the further development of the strategy. MPAG also called for a review of training and capacity development efforts coupled with an assessment of gaps to guide efforts to enhance the quality of primary health care with a commitment to equity and social justice.

- **Role of comparative assessment in the WHO evaluation of vector control products:** MPAG recognized the progress made by WHO on this subject since the October 2021 meeting and agreed with the underlying value of these non-inferiority tests as a mechanism for providing additional clarity to inform the procurement of new (second-in-class) vector control products. MPAG believed that the products being considered as second-in-class by non-inferiority evaluations need to meet all functionality requirements defined in the intervention definition. For LLINs, this means that products must be both wash-resistant and durable.
- **WHO Guidelines for malaria:** MPAG commended the Global Malaria Programme on the considerable progress made and on the draft treatment recommendations presented. MPAG emphasized the need for timely guideline updates, particularly as drug resistance has been identified as a major threat to progress. MPAG commended the implementation of this format of “living guidelines”, which allows for rapid updates, but commented that the document remains long and complex and suggested efforts to simplify the presentation.
- **Optimizing uptake of WHO guidance on malaria:** MPAG congratulated WHO on the dissemination activities undertaken so far and the additional activities planned to ensure uptake of WHO guidance on malaria. MPAG stressed the need to also address the issue of utilization by regularly assessing access and uptake by different stakeholders and using the information for improvement of dissemination strategies. The need for clear country-level dissemination channels was emphasized, and the need for national malaria programmes to continuously update their national and subnational mailing lists was also highlighted.
- **Uptake of chemoprevention recommendations:** MPAG acknowledged the substantial investments made to develop guidance in support of country malaria responses, and the efforts made to support country-level dissemination and uptake. However, they emphasized the importance of in-person discussions with national malaria programmes and country stakeholders during regular regional and in-country malaria meetings. Members emphasized the importance of tailoring activities to specific audiences and advised that some dissemination activities should target political leaders to obtain their buy-in and ensure that malaria remains a priority. MPAG further highlighted the need to place emphasis on competency-based capacity-building, including community and stakeholder engagement as well as coordination of the malaria response with relevant sectors.
- **RTS,S malaria vaccine roll-out:** MPAG noted that, considering that RTS,S is a new vaccine with a different administration schedule compared to other vaccines, its implementation in the pilot implementation countries has been a success, with coverage for the first dose at 74–84% in the first six months of 2022. MPAG remained concerned about the shortage of vaccine doses. Given the vaccine shortage and the urgent need to deploy the vaccine, the manufacturer should scale up vaccine production as quickly as possible. MPAG members also confirmed that the malaria vaccine is an intervention that should be added to the comprehensive control strategy, alongside continued vector control, personal protection including chemoprevention programmes, environmental interventions and other approaches.

- **Malaria elimination and technical consultation on prevention of re-establishment of malaria:** MPAG appreciated the update on malaria elimination and noted progress in many countries and the need to investigate and respond to resurgence in others. Of particular concern was the increased number of cases in several countries of the Americas. Special attention will need to be given to the different requirements for preventing the re-establishment of *P. vivax*. MPAG strongly supported both the need for a technical consultation on the prevention of re-establishment of malaria and the process that has been initiated for its development.
- **Global framework for the response to malaria in urban areas:** MPAG welcomed the content of the Framework, which acts as both an advocacy and a guidance document. MPAG acknowledged that tackling urban malaria will require microstratification of intervention strategies, including some interventions for which there is presently limited evidence of effectiveness and highlighted the importance of having different discussions for *P. vivax* and *P. falciparum*. It will be important for the Urban Framework to encourage surveillance activities that monitor the effectiveness of interventions and the distribution and behaviours of vectors, particularly the emergent threat posed by the invasion of the urban malaria vector *An. stephensi*. The Framework also acknowledges the growing challenge of other vector-borne diseases in the urban landscape, highlighting a need for an integrated approach to vector control in urban areas. MPAG emphasized that a critical step following the launch will be to support ongoing dissemination and strong engagement across all sectors and stakeholders.
- **Rectal artesunate (RAS) for severe malaria:** MPAG highlighted that this is an important and urgent review given that the malaria-endemic countries that have yet to introduce the intervention are awaiting further guidance from WHO before deploying RAS. MPAG members highlighted that the main issue is not RAS per se, but rather more broadly how to ensure that there is a continuum of care. Of particular importance are questions on the presence and functionality of the referral system where RAS is deployed. MPAG emphasized the importance of coordinating with other WHO departments focused on primary health care and mother and child health to ensure the successful implementation of this intervention. It was agreed that the Global Malaria Programme should inform MPAG of the outcome of the technical meeting as soon as it is available.
- **Pfhrp2/3 gene deletion issues:** MPAG congratulated the Global Malaria Programme on the progress over the last six months in standardizing *pfhrp2/3* deletion detection and on work to modify and update the Malaria Threats Map. MPAG recognized that the extent of *pfhrp2/3* gene deletions throughout Africa is not fully understood because of the limited sampling in many regions. Efforts to expand molecular surveillance in Africa should facilitate the development of a more comprehensive picture, and WHO should work closely with other stakeholders to make this a clear use case. Global funders should consider additional emphasis on supporting malaria genomic surveillance because of the increased importance for national malaria programmes.
- **An. stephensi in Africa and the WHO response:** MPAG recognized the progress made by the Global Malaria Programme in efforts to address the invasion of *An. stephensi*. In particular, MPAG was pleased to see a more considered approach that recognizes the risk of not paying sufficient attention to the problem as well as the risk associated with paying too much attention to it. It was noted that the response to *An. stephensi* should be backed by field data on the basic biology of the vector, the extent of its spread and its contribution to malaria transmission in different settings. MPAG suggested that WHO should continue to pay special attention to Eastern Africa where *An. stephensi* is geographically coincident with other biological threats to malaria.

## BACKGROUND

The World Health Organization (WHO) Global Malaria Programme convened the Malaria Policy Advisory Group (MPAG) for its 22nd meeting via a virtual platform on 11–13 October 2022. MPAG convenes twice annually to provide independent strategic advice to WHO on technical issues related to malaria control and elimination. MPAG was also convened for an ad hoc meeting on 24 August to provide input on the draft *Strategy to respond to antimalarial drug resistance in Africa*. The meeting summary is available in the Session 1 pre-reads. Over the course of the two days of open meetings, 19 MPAG members, national malaria programme managers, the WHO Secretariat and over 217 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 three.

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. Thirteen members reported interests; the full report is available on the meeting website. No MPAG members reported specific conflicts of interest relating 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 was presented on behalf of both acting Directors and covered progress since the last MPAG meeting on 23–24 March 2022 and included updates on normative guidance, meetings, publications, technical updates and country support.

The Global Malaria Programme's normative work comprises three steps in the pathway: better anticipate, develop recommendations and optimize uptake, with a feedback loop to improve the overall process.

In the "better anticipate" space, three preferred product characteristics (PPCs) were published: (i) endectocide and ectocide products for malaria transmission control; (ii) indoor residual surface treatments for malaria transmission control; and (iii) malaria vaccines. Five additional PPCs are in development: (i) tests for glucose-6-phosphate dehydrogenase (G6PD) activity; (ii) monoclonal antibodies; (iii) medicines for chemoprevention; (iv) tests for *Plasmodium vivax* recent infection; and (v) outdoor malaria vector control. In addition, the malaria department has contributed, together with the Prequalification Team, to the WHO coordinated scientific advice on artemolane-piperazine, artemether-lumefantrine-amodiaquine and ganaplacide-lumefantrine (solid dispersion formulation).

In the area of recommendation development, two updates to the *WHO Guidelines for malaria (1)* were published: revisions to the vector control recommendations in March, and new and revised recommendations on chemoprevention, mass drug administration and elimination in June. Planning is under way for WHO review of the next malaria vaccines, which could help to increase supply and reduce cost. The most advanced late-stage candidate is R21/MatrixM, and phase 2 data in seasonal use indicate that vaccine efficacy may be similar to that of RTS,S/AS01 in seasonal use. To support the optimized uptake of malaria guidance, the Dissemination Taskforce has met twice, with representation from all regions and partner organizations.

Technical updates were provided on vector control, drugs and diagnostics, drug efficacy and strategic information for response. Notable achievements in vector control include advances in the implementation of the District Health Information Software 2 (DHIS2) modules, insecticide resistance monitoring and new approaches to guide the prioritization of funding for vector control. In addition, an initiative on *Anopheles stephensi* was launched in September to coordinate the surveillance and response to this invasive vector species in Africa. The new classification of G6PD genetic variants is anticipated to be published in the WHO Bulletin. The new classification is based on an extensive review of the literature on the most common variants and incorporates MPAG's previous feedback to inform recommendations and test performance requirements.

The *Strategy to respond to antimalarial drug resistance in Africa* was endorsed by MPAG at an ad hoc meeting in August, and its launch is planned, together with the WHO Antimalarial Resistance Department, during Antimicrobial Awareness Week in November. The Strategy includes 20 interventions clustered in four pillars of interventions to be prioritized and targeted through country assessment: (i) strengthening the surveillance of antimalarial drug efficacy and resistance; (ii) optimizing and better regulating the use of diagnostics and therapeutics to limit drug pressure through pre-emptive measures; (iii) reacting to resistance by limiting the spread of antimalarial drug-resistant parasites; and (iv) stimulating research and innovation to better leverage existing tools and develop tools against resistance. Notable achievements in strategic information for response include updates to the DHIS2 aggregate toolkit, risk mapping for country stratification to be expanded to other high-burden countries and the finalization of the *Global framework for the response to malaria in urban areas* (2).

Other areas of intense work have supported implementing the *Framework for the allocation of limited malaria vaccine supply* (3) and the development of the *World malaria report 2022*, which will highlight insecticide-treated nets (ITNs), research and innovation, the *Strategy to respond to antimalarial drug resistance in Africa*, surveillance assessments, vaccine roll-out and the effects of the coronavirus disease (COVID-19) pandemic, and will include a supplement on the malaria situation in Nigeria.

Country support has focused on the "High burden to high impact" (HBHI) approach and countries working towards malaria elimination. Sudan has adopted the HBHI approach and is planning a high-level launch. There has been an assessment of the approach in six countries with support from the RBM Partnership to End Malaria's Country/Regional Support Partner Committee, finalization of data repositories and a data deep-dive workshop in Nigeria. Support has also been provided for malaria in humanitarian emergencies, including support to the Tigray Region in Ethiopia and to Pakistan. The malaria elimination course was published on the OpenWHO platform. The Technical Advisory Group on Malaria Elimination and Certification was convened for its first meeting in September, combining the functions of the previous Malaria Elimination Certification Panel and Malaria Elimination Oversight Committee.

## SUMMARY OF THE MPAG SESSIONS

### HBHI approach: progress, challenges, lessons learned and way forward

**Background:** The Global Malaria Programme and the RBM Partnership to End Malaria launched HBHI in 2018, recognizing that decades-long progress towards the morbidity and mortality goals for 2020 (40% reductions) in the *Global technical strategy for malaria 2016–2030 (4)* had stalled, particularly in the countries bearing the greatest burden of malaria. Through high-level consultation and extensive partnership, the approach supports country-led malaria programmes in India and the 10 African countries with the highest case and death numbers. HBHI rests on four pillars: political will, strategic information used for targeted malaria programming, better guidance, and partnership and coordination. While acknowledging the progress and need to expand beyond the original 11 countries to include others with similar high malaria incidence and death rates, several key challenges were noted. These include:

- slowed momentum due to COVID-19, which has disrupted service delivery, supply chains and in-person technical briefings for national programme managers;
- minimal translation of political will and leadership into increased domestic funding and general acceptance of intolerable levels of malaria;
- continued reliance on burden estimates in the face of inadequate, incomplete and untimely surveillance data;
- technical and management capacity limitations in national and subnational health authorities; and
- the inability to galvanize a multisectoral, whole-of-society response in all but a handful of small-scale settings.

**MPAG conclusions:** MPAG members noted the progress and challenges faced by the approach and commended WHO, national authorities and malaria programmes, and partners for persevering in the face of the pandemic and related supply-chain disruptions. However, it was noted that the immense support that came from all sectors to deal with Covid-19 had tended to lead to a shift in focus away from the 'everyday' public health problems such as malaria raising concerns about the ability to continue to focus high level political support to address this important public health priority. Members particularly noted the need for multisectoral approaches and encouraged the specific inclusion of the education sector, private medical and pharmaceutical providers, and communities. Others were concerned to learn that malaria-specific investments from national governments and some bilateral partners were static or in decline. This was one of a number of useful reflections of the "Rethinking malaria" initiative, which should be a useful resource when shaping the future of the HBHI approach. Members also emphasized the need for capacity development efforts beyond the national programme level to reach subnational and district leaderships in health and other sectors, and restated an interest in a review of WHO's malaria-related capacity initiatives, coordinated with the Special Programme for Research and Training in Tropical Diseases and the RBM Partnership to End Malaria. At least one member called for more country- and context-specific attention to urgently address the highest burdens in the Democratic Republic of the Congo and Nigeria.

MPAG called for a review of training and capacity development efforts coupled with an assessment of gaps to guide efforts to enhance the quality of primary health care

with a commitment to equity and social justice. MPAG further recommended that the HBHI approach revisit and draw on the outputs from the “Rethinking malaria” exercise to guide the further development of the strategy, for example, by identifying and supporting entrepreneurship, research and development, and manufacturing in endemic countries that contribute to addressing local malaria challenges as a mechanism for helping to ignite cross-sectoral political commitment and by helping to ensure more robust funding from national programmes and global partners. MPAG recognized the importance of a broader engagement in the malaria response, and recommended that WHO document examples of effective cross-cutting and multisectoral approaches to malaria. The good examples of engaging colleagues from health systems on the development of the Global framework for the response to malaria in urban areas should be extended to all of WHO’s malaria work.

## The role of comparative assessment in the WHO evaluation of vector control products using non-inferiority analysis for products of the same class

**Background:** Since the discontinuation of the WHO Pesticide Evaluation Scheme in 2017, the WHO vector control evaluation process and the Global Malaria Programme guidelines development process have evolved significantly. Explicit demonstration of an intervention’s public health value (epidemiological impact) and formulation of a WHO recommendation for the intervention is essential and explicit. ITNs have been consolidated into three intervention classes (to be covered by WHO recommendations), meaning that fewer trials with epidemiological end-points will be needed overall compared to if innovative products were all considered individually. In turn, there is a need for some form of assurance that a WHO recommendation – formulated by drawing on epidemiological impact data from at least two trials deploying a “first-in-class” product – applies to a “second-in-class” product. At the request of MPAG, non-inferiority assessment using one or more entomological end-points has been explored using pyrethroid-piperonyl butoxide (PBO) nets as a case study. In October 2021, the findings and recommendations from the second technical consultation on non-inferiority were presented to MPAG and endorsed.

Over the last year, WHO has held internal discussions regarding the implementation of non-inferiority assessments as part of the WHO vector control evaluation process, including: the potential value as a complement to the processes of prequalification and recommendation development; the communication of findings; the translation of such data into decisions; and the respective roles of the different WHO departments in evaluating such data. To guide internal WHO discussion on implementation, it was agreed that WHO’s approach to assessing the non-inferiority of vector control interventions needs to remain exploratory, with a focus on ITNs formulated with non-pyrethroid active ingredients alone or in combination with a pyrethroid. The internal discussion identified principles, assumptions, and potential challenges, and agreed on a plan for implementation and next steps.

**MPAG conclusions:** MPAG recognized the progress made by WHO on this subject since the October 2021 meeting and agreed with the underlying value of these non-inferiority tests as a mechanism for providing additional clarity to inform the procurement of new (second-in-class) vector control products. However, additional concerns and requests for clarification were made as follows.

- Long-lasting insecticidal nets (LLINs) are defined based on their wash resistance and field durability, with modelling studies indicating that more durable nets would be more cost-effective (5). However, net retention is suboptimal in some countries within the defined expected life of an LLIN (6,7).

- Given that the quality of products is integral to performance, product quality and, in the case of LLINs, both durability and bioefficacy are critical and each should be assessed.
- It was also noted that WHO recognized the role of LLINs in feeding inhibition (which the tunnel test was created to assess), and that this function of an LLIN is considered as a secondary endpoint in assessments of non-inferiority (8).
- Pyrethroid-PBO nets, dual active ingredient nets and pyrethroid-only nets are three types/categories of LLINs that fall within one class of vector control products. MPAG was unclear as to whether there is a unified approach for non-inferiority evaluation of all products within a class or whether the unique attributes of products will require different assessments of non-inferiority. Some MPAG members expressed questions about the classification system originally endorsed in the May 2020 meeting (9) and requested to continue annual updates on the data available to inform a potential update to the classification.
- MPAG was concerned that non-inferiority evaluations that avoided the issues of data comparability introduced by testing different products in different sites at different times would also fail to capture the performance of new products in different ecologies with different vector species. These gaps could lead to universal deployment recommendations not backed by data.
- As it was stated that WHO does not have the capacity to undertake additional non-inferiority assessments, MPAG requested clarification on who would be responsible for such assessments. MPAG noted the proposal to have periodic comparative evaluations of different products as a way to generate data that would be acceptable to all parties. Some MPAG members questioned the design of the non-inferiority assessments and the example of the approach used for PBO studies with two different study sites as an appropriate design.
- There is a need to indicate that the collection of data to assess non-inferiority should be included in the workstream to generate data for the prequalification dossier.
- WHO stated that “if durability data were added to the non-inferiority assessment approach and if this were to require field studies after two to three years of field use, then we would envisage that these data could be added at a later stage so as to not delay market entry”. MPAG cautioned that this approach could introduce inferior products into the market, with corresponding increases in malaria cases, as was seen in Papua New Guinea when nets that did not retain adequate insecticide were widely distributed (10).
- MPAG opined that all product data from non-inferiority trials should be open and available for the community to consider (and published).

MPAG believed that the products being considered as second-in-class by non-inferiority evaluations need to meet all functionality requirements defined in the intervention definition. For LLINs, this means that products must be both wash-resistant and durable. Multiple concerns were raised by both MPAG members and observers regarding the process (the if, when and how) of durability assessment of LLIN candidate products and the relationship of such assessments to the non-inferiority evaluation of bio-efficacy (killing and knockdown). MPAG, therefore, requested a clarification on the process by which second-in-class candidate LLINs are selected for non-inferiority determination. MPAG also requested that appropriate guidance be included on how the non-inferiority test results should be interpreted by users (e.g. national malaria programmes and procurement agencies).



## Update on WHO Guidelines for malaria

**Background:** Developing recommendations is the second step in the WHO pathway to support national ministries of health as they develop policies and strategic plans. The *WHO Guidelines for malaria* are available from the WHO website in PDF format, are hosted on the MAGICapp platform and have been translated into French, Arabic and Spanish. Three updates have been published in 2022 to date and three Guideline Development Groups (GDGs) continue to work on recommendations for vector control, diagnosis and treatment.

Updates to the vector control section were published in March, including an update of the conditional recommendation for pyrethroid-PBO nets with moderate-certainty evidence and considerations of the high unit cost compared to pyrethroid-only nets. Two new recommendations were added for vector control in humanitarian emergencies: a strong recommendation for ITNs (high-certainty evidence) and a conditional recommendation for indoor residual spraying (very low-certainty evidence). The next meeting is planned for November and will include assessment of evidence on topical repellents, residual surface treatments and dual active ingredient nets for anticipated publication in quarter one of 2023.

The GDG for diagnostics will meet for the first time later this year for a scoping meeting to prepare recommendations for near-patient G6PD tests to support the administration of 8-aminoquinolines for prevention of *P. vivax* relapse. The target product profiles and revised classification based on reviews of genotype (variant)/phenotype (G6PD activity) were completed in 2022 and are critical to inform the acceptable characteristics of tests. The Global Malaria Programme is working closely with the Prequalification Team to support independent evaluation of the only candidate near-patient G6PD test. A model is being used to predict the impact of varying test characteristics on risk of haemolysis and relapse to support GDG decision-making.

The following recommendations developed by the GDG for chemotherapy were approved by the WHO Guidelines Review Committee and are being finalized for publication in the coming weeks: (i) artesunate-pyronaridine is recommended as an artemisinin-based combination therapy option for the treatment of uncomplicated *P. falciparum* malaria (strong recommendation for, low-certainty evidence); (ii) pregnant women with uncomplicated *P. falciparum* malaria should be treated during the first trimester with artemether-lumefantrine (strong recommendation for, low-certainty evidence); (iii) with regards to primaquine treatment to prevent relapse, 0.5 mg/kg/day for seven days is recommended to treat *P. vivax* or *P. ovale* malaria in children and adults (except pregnant women, infants aged < 6 months, women breastfeeding infants aged < 6 months, women breastfeeding older infants unless they are known not to be G6PD-deficient, and people with G6PD deficiency; strong recommendation for, very low-certainty evidence), however, (iv) WHO recommends against using primaquine 1.0 mg/kg/day for seven days to treat *P. vivax* or *P. ovale*.

**MPAG conclusions:** MPAG commended the Global Malaria Programme on the considerable progress made and on the draft recommendations provided. Of particular note was the approval of the chemotherapy guidelines by the Guidelines Review Committee and the anticipated publication. MPAG emphasized the need for timely guideline updates, particularly as drug resistance has been identified as a major threat to progress. In terms of G6PD deficiency testing, MPAG encouraged the team to reach out to other scientists working on this topic to comprehensively consider all approaches. MPAG commended the implementation of this format of “living guidelines”, which allows for rapid updates, but commented that the document remains long and complex and suggested efforts to simplify the presentation.

## Optimizing uptake of WHO guidance on malaria and the work of the Dissemination Taskforce

**Background:** The third step in the pathway is to optimize the uptake of guidance by improving the way it is shared and updated, guided by the Global Malaria Programme's dissemination strategy. The main target audience consists of staff working within ministries of health, national malaria programmes and implementing agencies. The key digital platforms include the WHO website, MAGICapp and the WHO Malaria Toolkit mobile app. A new page on the website clearly describes how to access WHO malaria guidance through the digital platforms and is available in multiple languages. A comprehensive information package was released in June 2022 to support the launch of new guidance on malaria chemoprevention and elimination. Information notes directed readers to MAGICapp and related technical content on the website.

The *WHO Guidelines for malaria* were first published on the MAGICapp platform in English in February 2021 and are now also available in French, Arabic and Spanish. As of early October 2022, there had been more than 46 000 page views of the English and French consolidated guidelines on MAGICapp, and more than 170 000 PDF downloads from the platform, indicating that page views and PDF downloads have more than doubled since March 2022. The expanded version of the WHO Malaria Toolkit app was launched in 2020 with a section focused on malaria guidance in order to provide a user-friendly resource for rapidly verifying data and guidance in the field. The app is currently available in English and translations are planned for 2023.

A new approach to support the dissemination of guidance is the development of short, animated videos that describe WHO malaria recommendations in a simple and visually engaging way. The first video, on histidine-rich protein 2 (HRP2) gene deletions, was launched in 2021; new videos focused on seasonal malaria chemoprevention, perennial malaria chemoprevention and monitoring insecticide resistance were launched in 2022. WHO's malaria guidance and dissemination platforms are shared through a number of distribution channels, including an internal mailing list of 250 WHO colleagues; an external mailing list that reaches over 8000 subscribers, including technical partners and national malaria programmes; and social media and partner networks. A survey on digital dissemination platforms was launched in September to assess whether WHO's malaria stakeholders are aware of the dissemination platforms, the usability of the platforms, whether there are any suggestions for improvement and whether there are other digital platforms that should be considered.

An informal malaria Dissemination Taskforce was established in late 2021 to guide and support WHO's malaria guidance dissemination efforts. More than 25 members, including WHO staff, country-based malaria focal points and partners, met three times in 2022 to provide feedback on WHO's dissemination strategy and activities. Key deliverables have been the publication of the Arabic and Spanish translation of the WHO Guidelines for malaria, the development of slides with links to the dissemination platforms to include in technical presentations, the finalization of videos, a push notification added to the mobile app, and a semi-annual communication of what guidance is anticipated. Work is ongoing to amplify WHO malaria guidance through partner networks, to update stakeholder mailing lists, to develop new dissemination tools, and to monitor and track the uptake of WHO malaria guidance. The team also noted that there are additional barriers to the uptake of malaria guidance that will require additional collaboration and support, including limited capacity and funding, the need for greater programme integration and multisectoral collaboration, limitations in capacity at country level to adapt the guidance to the local context, and the lack of local data to guide the adoption and adaptation of global guidance.

**MPAG conclusions:** MPAG congratulated WHO on the dissemination activities undertaken so far and the additional activities planned to ensure uptake of WHO guidance on malaria. MPAG members also acknowledged the establishment of multiple digital platforms for the dissemination of guidance and work to collaborate with other global partners to utilize their platforms.

MPAG further noted that a survey has been posted to solicit feedback from target audiences and partners on how to improve the dissemination channels and reach. MPAG stressed the need to also address the issue of utilization by regularly assessing access and uptake by different stakeholders and using the information for improvement of dissemination strategies. The need for clear country-level dissemination channels was emphasized, and the need for national malaria programmes to continuously update their national and subnational mailing lists was also highlighted. MPAG members also acknowledged the plan to develop a dissemination monitoring and evaluation framework and pointed out the need to cover uptake, using valid and practical indicators.

MPAG further highlighted the need to place emphasis on competency-based capacity-building, including community and stakeholder engagement as well as coordination of the malaria response with relevant sectors. Members hoped that the ongoing review of capacity-building programmes for malaria control would take this important issue into consideration.

## Feedback on the uptake of chemoprevention recommendations

**Background:** The new and updated recommendations for malaria preventive chemotherapies in the *WHO Guidelines for malaria* were published in June 2022. Key dissemination events included the circulation of policy recommendations and frequently asked questions to ministries of health in the WHO African and Eastern Mediterranean Regions, and updates provided at four RBM Partnership to End Malaria programme manager meetings in Africa from June to August. WHO regional teams have engaged with national malaria programmes and have recirculated the frequently asked questions in response to requests for clarification. An in-person workshop for further dissemination to national malaria programmes is also planned for the Eastern Mediterranean Region in December 2022. Some general observations on the process to date include the following.

- Several clarifications are needed relating to the implications of policy recommendation for countries' respective contexts.
- Member States are encouraged to consider policy recommendations during their respective national health/malaria policy updates and strategy reviews through the deliberations of national malaria technical working groups where these exist, and during future consultations on intervention re-stratification.
- Greater flexibility presents greater complexity in decision analysis. The subsequent national policy adaptation processes at country level needs to consider asymmetries in information access and be aligned with who decides what and at what level decisions are made;
- National malaria technical working group reviews need to reflect on the implications of policy recommendations at three levels:
  - potential contributions to accelerating the attainment of existing strategic objectives: (i) attainment of national malaria plan objectives and targets and (ii) planning cycles of national strategic plans;

- implications of policy recommendations for pre-existing strategic approaches and revisions are required; and
- implications of any recommended amendments for action that need to be taken at the national health policy level, e.g. regulatory policies, essential medicines lists, drug policy, minimum health service packages and so on, including financial aspects.

The WHO Regional Office for Africa is investing in the development of a framework for policy adaptation and implementation of perennial malaria chemoprevention for malaria technical working groups and stakeholders. The framework is a decision tree of key considerations in adapting the policy to local contexts, informing recommendations for ministry of health policy and national malaria programme strategy review on perennial malaria chemoprevention. Integration will be explored as part of the policy dialogue associated with the roll-out of the malaria intervention stratification manual when available, the development of recommendations, orientation for implementation and responses to requests for clarification.

**MPAG conclusions:** MPAG acknowledged the substantial investments made by WHO to develop malaria guidance in support of country malaria responses, and the efforts made to support country-level dissemination and uptake of the guidance. However, they emphasized the importance of in-person discussions among staff of WHO, national malaria programmes and country stakeholders during regular regional and in-country malaria meetings. Members emphasized the importance of tailoring activities to specific audiences and were of the view that some of the dissemination activities should be targeted at political leaders in order to obtain their buy-in and ensure that malaria remains a priority in the areas where it remains a public health challenge. In addition, MPAG pointed out that reaching front-line workers with the guidelines and ensuring that they are taken into consideration by national programmes in the development of national strategic plans would require the operationalization of the WHO guidance in national guidelines.

Additional barriers to the dissemination of guidelines and further downstream work on adopting, adapting and using guidelines were highlighted during the discussion, including: challenges affecting the development of national-level guidelines (adequate understanding of developed guidance should be ensured); the high turnover of national malaria programme staff; challenges in the dissemination and operationalization of national guidelines; and accountability for uptake.

MPAG recommended that WHO:

- ensure that all staff are aligned on the guidelines to ensure a coherent WHO message;
- set up easy channels for obtaining countries' feedback if they encounter difficulties in understanding the material in WHO guidance documents;
- maximize the opportunity of HBHI to support countries in adopting and adapting guidelines and developing evidence-based country guidelines;
- organize more technical assistance to national malaria programmes through WHO country offices and country-level advisory groups of national experts;

in addition to recommendations on malaria diagnosis, treatment, and other control interventions, develop guidance material to support the acquisition and strengthening of competency based soft skills in areas such as partnership development, advocacy, intersectoral collaboration, coordination, community engagement, and resource mobilization as part of the ongoing review of capacity building for malaria control and elimination.

## Update on the RTS,S/AS01 malaria vaccine roll-out

**Background:** In October 2021, following a joint review by MPAG and the Strategic Advisory Group of Experts on Immunization, WHO recommended that the RTS,S/AS01 malaria vaccine be used for the prevention of *P. falciparum* malaria in children living in regions with moderate to high transmission, as defined by WHO. As of early September 2022, more than 3.4 million vaccine doses had been administered with more than 1.1 million children receiving at least one dose in areas of Ghana, Kenya and Malawi, where the vaccine has been implemented since 2019 as part of the Malaria Vaccine Implementation Programme (MVIP). The malaria vaccine is now included as part of Gavi, the Vaccine Alliance's portfolio, with an initial investment of US\$ 155.7 million for the 2022–2025 period. The first opportunity to apply was in September 2022 for MVIP countries and will be in January 2023 for other eligible countries. To date, at least 24 countries have expressed interest in introducing the malaria vaccine.

The United Nations Children's Fund announced a contract award that secures supply for further roll-out of 18 million doses for 2023–2025. However, low volumes have resulted in an initially high cost at €9.30 per dose. Supply constraints are anticipated to continue for the next few years. The ongoing product transfer of RTS,S/AS01 to Bharat Biotech and the potential entrance of a second malaria vaccine that is currently in phase 3 trials could increase supply availability and reduce the price. Gavi will soon be publishing its market-shaping roadmap, which outlines how the malaria vaccine market should evolve in the short- and long-term to increase supply and reduce cost. The Framework for the allocation of limited malaria vaccine supply offers guidance on the global allocation of RTS,S/AS01, and other malaria vaccines as they become available. The Framework also provides guidance on prioritization of areas for vaccination within countries until supply constraints can be fully resolved. The Framework outlines governance principles, ethical principles for allocation, additional key considerations and a foundational value of solidarity. The first priority principle is greatest need: allocate the vaccine to countries with areas of greatest need, where the malaria disease burden in children and the risk of death are high. Health system weaknesses, poor access to prevention and prompt treatment, and unjust disparities within the system increase the need for additional protection through the malaria vaccine. To enable cross-country comparison, the proxy measure for greatest need is a composite index that combines subnational estimates of the prevalence of *P. falciparum* infections in children aged 2–10 years and the estimated under-5 mortality rate. Interested countries will identify the areas of highest burden and need within their own borders based on best available local evidence and the broader context of subnational tailoring of different malaria interventions. A key consideration is to continue vaccination in areas of the MVIP countries where the vaccine has already been introduced. Initially, if there are unmet vaccine requests for greatest need (category 1) areas across multiple countries, no single country should receive more than 20% of the total available supply.

Gavi invites countries to describe the full scope of vaccine supply need in their application, alongside a stratification by category of need, but for the time being, Gavi will support only four doses per child. The Framework is expected to be applied following each Gavi application round, and firm vaccine allocation decisions will initially be limited to category 1 (greatest need) areas and subject to the solidarity cap of 1 million doses per year for countries with large category 1 areas. If supply is insufficient to satisfy all category 1 areas from countries with successful applications, the second priority allocation principle (maximize health impact – using as a proxy the drop-out rates between the third dose of diphtheria-tetanus-pertussis vaccine and the first dose of measles-containing vaccine) will be applied to establish the country order of priority. Three multi-country technical assistance workshops have been offered in 2022 to support countries to develop quality applications for the malaria vaccine.

**MPAG conclusions:** MPAG noted that, considering that RTS,S is a new vaccine with a different administration schedule compared to other vaccines in the Expanded Programme on Immunization, its implementation in the MVIP countries has been a success, with coverage for the first dose at 74–84% in the first six months of 2022. MPAG remained concerned about the shortage of vaccine doses. Only 18 million doses will be available for 2023–2025. Of these, approximately 6–7 million doses will likely be required to continue vaccination services in the MVIP countries. Therefore, there will be about 11 million doses available over the next three years for new introduction. As there are at least 24 countries interested in implementing the malaria vaccine, it is important to manage expectations, as access to the vaccine is not guaranteed during the initial years of roll-out.

The current price is estimated at €9.30 per dose, which is higher than some might have expected. Nevertheless, even at this higher cost, RTS,S remains a cost-effective intervention based on comparisons with other recently introduced vaccines. Given the vaccine shortage and the urgent need to deploy the vaccine, the manufacturer should scale up vaccine production as quickly as possible.

MPAG members looked forward to the publication of final longest-term results of the MVIP, specifically the results on coverage and mortality (estimated prevented deaths) and previous issues of concern such as those related to gender-specific mortality and meningitis. The surveillance will be completed at the end of 2023 and the analysis is anticipated in 2024.

The *Framework for the allocation of limited malaria vaccine supply* states that the composite index (*P. falciparum* parasite rate and under-5 mortality rate) will be used to identify the areas of greatest need. The Framework also indicates that countries are encouraged to use their best available local evidence, including malaria incidence and severe malaria data, to establish the categorization of needs. MPAG asked for clarification on the methodology to reconcile local data with the proposed global proxy measure.

The foundational value of solidarity defined in the Framework establishes that individual countries should initially not receive more than 20% of the available supply in order to enable a larger number of countries with high need areas to access the vaccine. MPAG members expressed concern given the shortage of supply and the malaria situation in HBHI countries. Some members remained concerned that by restricting the maximum number of doses per country, large countries would only be able to provide the vaccine to a small portion of their population. MPAG emphasized the need for increased production and supply, and for the distribution of vaccines to be as equitable as possible.

The countries with the greatest need may be those with the weakest health services (lower quality primary health care, lack of trained personnel, lack of cold chain, etc.). Accordingly, there is a need for additional support to reach areas with poor health services, as these are probably the areas with the greatest need for the vaccine.

MPAG members also confirmed that the malaria vaccine is an intervention that should be added to the comprehensive control strategy, alongside continued vector control, personal protection including established chemoprevention programmes, environmental interventions and other approaches.

## Update on malaria elimination and the technical consultation on prevention of re-establishment of malaria

**Background:** An update was provided on the progress of countries towards elimination and the health outcomes of the E-2020 Initiative that supported eight countries to achieve and maintain zero indigenous cases by the end of 2020 (Algeria, Belize, Cabo Verde, China, El Salvador, Iran [Islamic Republic of], Malaysia and Timor-Leste). The E-2025 initiative was launched in 2019 with three objectives: (i) to accelerate the elimination of indigenous malaria transmission; (ii) to certify countries as malaria-free after three years of zero indigenous transmission; and (iii) to support malaria-free countries to prevent re-establishment. Countries are continuing to make progress and it is anticipated that five countries may be certified as malaria-free by the end of 2023 (Azerbaijan, Belize, Cabo Verde, Iran [Islamic Republic of] and Tajikistan).

The two technical advisory groups supporting malaria elimination have been combined to form the Technical Advisory Group on Malaria Elimination and Certification. The group first met in September 2022 and has five functions: (i) to provide independent evaluation and advise WHO whether a country should be certified as malaria-free based on WHO criteria or whether certification should be postponed; (ii) to review the data from countries that are certified as malaria-free on an annual basis and advise WHO on whether a country should be de-certified based on the WHO criteria; (iii) to provide support to WHO to resolve bottlenecks for malaria elimination at the country, regional and global levels; (iv) to provide advice to WHO on areas where new or improved policy recommendations or implementation guidance may be required; and (v) to provide other support and advice to WHO in the field of malaria elimination and prevention of re-establishment of transmission. Certification of malaria elimination missions to Azerbaijan and Tajikistan are taking place in October 2022.

The STOP Malaria programme was launched in 2019 to strengthen subnational technical and operational capacity to eliminate the last foci of malaria transmission. STOP Malaria consultants have supported Botswana, Cabo Verde, Ecuador, Eswatini, Namibia, Sao Tome and Principe, Suriname and Vanuatu. An evaluation is underway to conduct an impact assessment and effectiveness evaluation of STOP Malaria activities, to identify alternative scenarios to support malaria elimination at the subnational level and estimate related costs, and to make a cost-benefit comparison of the STOP Malaria programme with the proposed alternatives.

In June 2022, eight new recommendations for and against elimination were published in the *WHO Guidelines for malaria* and an online malaria elimination course was launched, with more than 8200 enrolments to date.

The fourth Global Forum of malaria-eliminating countries is planned for 24–26 January 2023 in Cape Town, South Africa with the theme of accelerating elimination to achieve the *Global technical strategy for malaria* milestones.

A new area of work will be the development of guidance on the prevention of re-establishment of malaria transmission. The technical consultation on the prevention of re-establishment of malaria transmission will be launched in January 2023 during the fourth Global Forum of malaria-eliminating countries. This will be followed by three virtual meetings in February and an in-person technical consultation in March. It is expected that the final document will be published by the end of 2023. The technical consultation will review the available data and evidence, practices, experiences and lessons learned in preventing the re-establishment of transmission in malaria-free countries or areas to achieve the following objectives.

- Provide guidance on how to improve the efficiency, effectiveness and sustainability of detection of malaria cases, including outbreak detection and response.
- Provide guidance on maintaining quality-assured diagnosis and case management.
- Provide guidance on integrating malaria activities into general health services and sustaining a malaria-free status through the process of building a resilient health system.
- Provide guidance on mitigating receptivity and risk of importation, and methods to monitor changes in receptivity, risk of importation and risk of re-establishment to inform a suitable mix of interventions.
- Provide guidance on leveraging multisectoral collaboration for the prevention of re-establishment of transmission.
- Define research priorities to inform the practice of preventing re-establishment of transmission.

**MPAG conclusions:** MPAG appreciated the update on malaria elimination and noted progress in many countries and the need to investigate and respond to resurgence in others. Of particular concern was the increased number of cases in several countries of the Americas. MPAG highlighted the importance of addressing *P. vivax* and *P. falciparum* separately, given their quite different behaviours. Special attention will need to be given to the different requirements for preventing the re-establishment of *P. vivax*.

At least two countries reporting many cases of simian malaria are listed as being close to elimination; therefore, it is important to give technical guidance to countries on continuing programmes to reduce morbidity from these causes of severe malaria and guidance on a communication strategy to cover the key issues. MPAG was advised that recommendations regarding *P. knowlesi* in Malaysia will be developed in discussion with country authorities next year.

MPAG strongly supported both the need for a technical consultation on the prevention of re-establishment of malaria and the process that has been initiated for its development. It was noted that prevention of re-establishment requires emphasis on different programmatic processes than may have been present in the elimination phase. Approaches to achieve elimination must be considered separately from approaches to prevent re-establishment. Much can be learned from the experience in China.

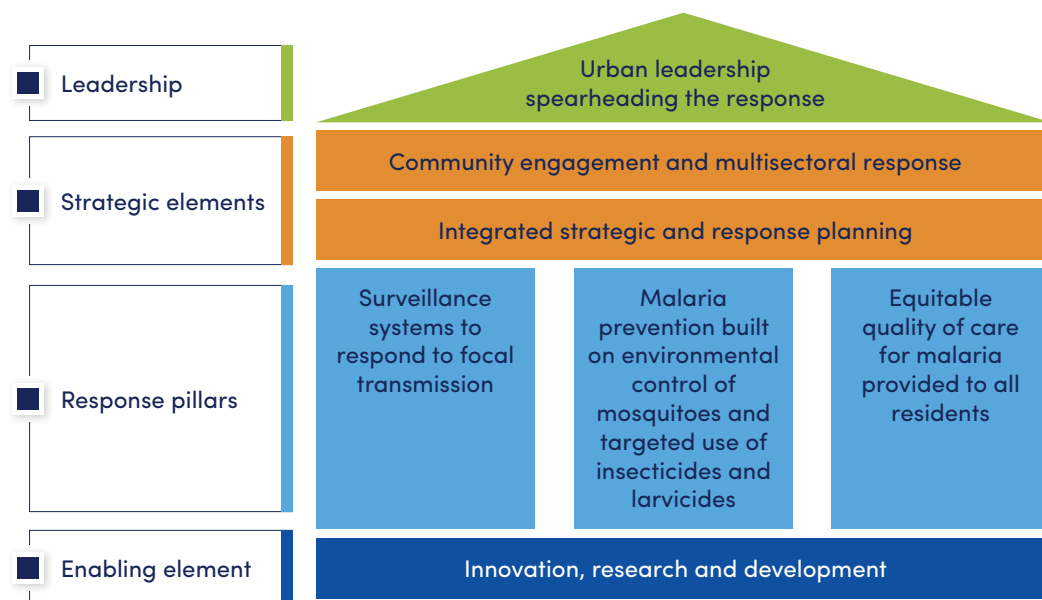
## **Update on the *Global framework for the response to malaria in urban areas***

**Background:** The aim of the Framework is to guide countries in developing policies, strategies and plans that are system-wide and multisectoral to effectively respond to malaria in urban areas, and to identify important knowledge gaps and define research priorities in the response to malaria in urban areas. The target audiences are national and urban government policy-makers; national and subnational malaria programmes; funders; development and implementation partners; private sector, civil society and advocacy partners; researchers; and communities. The Framework is built on five central themes: (i) prevention interventions and delivery; (ii) health care



delivery; (iii) urban governance, policies and planning; (iv) multisectoral response; and (v) surveillance, mapping and analysis. Its development included over 120 participants and about 30 consultations, and its anticipated launch is on 31 October 2022 at the World Cities Day event convened by the United Nations Human Settlements Programme. The Framework incorporates three response elements building on three pillars enabled by innovation, research and development (see **Fig. 1**).

**Fig. 1. Building blocks of the *Global framework for the response to malaria in urban areas***



Urban leadership spearheading the response addresses the role of urban leadership and governance, benefiting from alignment with international goals and integration with sustainable city growth and the [One Health approach](#), and includes mobilizing resources for urban malaria control. Community engagement is a process of continuous relationship-building in which those affected are central to decision-making, whereas a multisectoral response engages priority sectors that impact or are impacted by malaria. The Framework focuses on integration, digitalization, competencies and case-based surveillance with travel history as an ambition across all urban settings. Preventing malaria and delivering quality care in urban areas are both addressed across the continuum of tools and strategies available. The key steps to developing an urban malaria response plan include pre-planning, conducting a situation analysis, tailoring malaria interventions to clusters of transmission within urban settings (microstratification) and developing the response plan. Several areas were identified for further innovation, research and development.

**MPAG conclusions:** MPAG acknowledged the great effort made by the Global Malaria Programme in developing the *Global framework for the response to malaria in urban areas*. This global multidisciplinary consultation was supported by five specialized thematic area working groups in which several MPAG members actively participated.

Overall, the MPAG team welcomed the content of this needed Framework, which acts as both an advocacy and a guidance document. MPAG acknowledged that tackling urban malaria will require microstratification of intervention strategies, including some interventions for which there is presently limited evidence of effectiveness and highlighted the importance of having different discussions for *P. vivax* and *P. falciparum*. As such, the Urban Framework is based on broadly accepted global public health principles. It was acknowledged that this might appear to some readers as a departure

from the expected standard of evidence required for the development of WHO malaria-specific recommendations, which requires epidemiological evidence of effectiveness. MPAG advised the Global Malaria Programme to specify that when and where specific examples of interventions are provided that are based on first principles, that it be clear that such interventions do not necessarily constitute malaria-specific recommendations and official WHO guidance. As such, it will be important for the Urban Framework to encourage surveillance activities that monitor the effectiveness of interventions and the distribution and behaviours of vectors, particularly the emergent threat posed by the invasion of the urban malaria vector *An. stephensi* across Africa.

The Framework also acknowledges the growing challenge of other vector-borne diseases in the urban landscape, most notably dengue. Consequently, there is a need for an integrated approach to vector control in urban areas. Acknowledging that this is an area traditionally neglected by malaria programmes, MPAG emphasized that a critical step following the launch of the Framework will be to support ongoing dissemination and strong engagement across all sectors and stakeholders. Several specific comments were raised, mostly relating to areas in need of simplification (e.g. figures) and further clarification or expansion (e.g. India case study).

## Update on rectal artesunate (RAS) for severe malaria – independent review of evidence and field manual

**Background:** The main therapeutic objective of the treatment of severe malaria is to prevent the patient from dying; the secondary objectives are to prevent disability and prevent recrudescence. Death from severe malaria often occurs within hours of onset of symptoms or admission to hospital, so it is essential for therapeutic concentrations of a highly effective antimalarial to be rapidly achieved. Current recommendations on the treatment of severe malaria are to treat all patients with intravenous or intramuscular artesunate for at least 24 hours until oral medication, i.e., an artemisinin-based combination treatment (ACT), can be administered. In settings where severe malaria cannot be adequately managed but injections are available, patients should receive a single dose of intramuscular artesunate and then be referred to an appropriate facility for further care. Artemether or quinine should be used if artesunate is not available. In settings where intramuscular injections are unavailable, children under 6 should be treated with a single dose of RAS and referred immediately to an appropriate facility for further care. Where referral is not possible, rectal treatment should be continued until a complete course of an effective ACT (based on expert opinion) can be administered.

WHO convened a technical consultation in April 2021 to review lessons learned from the Community Access to RAS for Malaria (CARAMAL) project to develop operational guidance on the use of RAS as pre-referral treatment of severe malaria in children and reviewed the study results with MPAG. Following MPAG's advice, WHO published an information note in January 2022 with risk mitigation advice for countries as follows:

- Countries that have not yet introduced pre-referral RAS but are considering doing so should withhold implementation and await further guidance from WHO on the criteria that need to be met to ensure the safe and efficacious use of RAS.
- Countries that have already adopted and are deploying pre-referral RAS should urgently review in detail the conditions under which it is currently being used. This includes all three steps along the cascade of care: (i) diagnosis and administration of RAS; (ii) immediate referral; and (iii) complete treatment with at least 24 hours of injectable artesunate and a three-day artemisinin-based combination therapy. Countries that have already adopted pre-referral RAS

are encouraged to withhold further expansion of its use until they receive further guidance from WHO.

As indicated in the information note, the Global Malaria Programme is committed to conducting a formal evidence review and developing detailed guidance on the conditions under which the use of this tool can be implemented safely and effectively, in consultation with other relevant departments.

The Global Malaria Programme has convened an independent technical group to undertake a technical review of all publications and study reports on the deployment of RAS at the programmatic level to determine the factors required to safely and effectively deploy RAS as pre-referral treatment for severe malaria in areas where complete treatment of severe malaria is not immediately accessible. The outcome of the consultations will form the basis of a WHO field manual to facilitate effective deployment of pre-referral treatment (particularly RAS) in resource-limited malaria-endemic countries. A first meeting was held in September 2022 to review the currently available evidence and generate questions and requests for clarifications for the study teams. A second meeting is planned for October 2022 to review the available evidence and to generate practical guidance to enable safe and effective implementation of RAS for the pre-referral treatment of children with severe malaria. The field manual to support countries in the safe and effective deployment of pre-referral treatment is anticipated in February 2023.

**MPAG conclusions:** MPAG acknowledged the Global Malaria Programme's establishment of an independent technical group to review the evidence on RAS. Members noted that this was in line with MPAG's recommendation that the Global Malaria Programme, in consultation with other relevant departments, conduct a formal evidence review and develop detailed guidance on the conditions under which the use of this potentially life-saving tool can be implemented safely and effectively. MPAG noted that a first technical consultation to review several documents and formulate questions for the research groups had been held virtually in September 2022 with a follow-up meeting planned for October 2022.

MPAG highlighted that this is an important and urgent review given that the malaria-endemic countries that have yet to introduce the intervention are awaiting further guidance from WHO before adopting and deploying RAS. MPAG further noted that guidance on the use of RAS involves referral to a health facility where the patient can be treated with artesunate injection until oral treatment can be administered. However, in situations where referral is not possible for various reasons, the current recommendation to continue with RAS until oral treatment can be administered is based on expert opinion and not evidence. Members emphasized that following the review, further studies with appropriate study design should be commissioned, if required, to address any unanswered operational questions.

MPAG members highlighted that the main issue is not RAS per se, but rather more broadly how to ensure that there is a continuum of care. Of particular importance are questions on the presence and functionality of the referral system in each country where RAS is deployed. MPAG, therefore, emphasized the importance of coordinating with other WHO departments focused on primary health care and mother and child health to ensure the successful implementation of this intervention. Another important question is the potential impact that the implementation of RAS may have on the selection for partial resistance to artemisinin in areas where it has emerged. Moreover, the quality and stability of RAS should also be considered. It was agreed that, in view of the importance of this issue, the Global Malaria Programme should inform MPAG of the outcome of the technical meeting as soon as it is available, preferably before the next MPAG meeting.

## Update on *pfhrp2/3* gene deletion issues

**Background:** Accurate, timely diagnosis of malaria is critical to case management and is a key element in national and global malaria control and strategies for elimination. Rapid diagnostic tests (RDTs) detecting HRP2 have transformed the malaria diagnostic approach over the past 15 years, greatly facilitating access to diagnostic testing prior to treatment and strengthening surveillance efforts. However, this important tool is now under threat due to the emergence, and in some cases dominance, of *P. falciparum* parasites with HRP2 and HRP3 (*pfhrp2/3*) gene deletions that result in false-negative RDT results. Since the discovery of *pfhrp2/3* deletions in 2008, WHO, partners and research groups have been addressing this issue both in the laboratory and in the field. The WHO malaria RDT product testing programme made annual calls to test developers to invest in alternatives to HRP2-based tests to reduce the reliance on these products. However, only one *P. falciparum*-specific lactose dehydrogenase (pf-LDH)-based RDT has met the minimum performance requirements for the detection of *P. falciparum*, with additional tests in the WHO prequalification pipeline. In 2019, a global response plan was launched, laying out a core set of actions for WHO, scientists, ministries of health, implementing partners and manufacturers (11). In 2021, MPAG released a statement on the high prevalence of *pfhrp2/3* deletions in the Horn of Africa and beyond (12).

The response plan laid out four objectives, and significant progress has been made.

- **Objective 1:** Define the frequency and distribution of diagnostically relevant mutations in circulating *P. falciparum* strains. Data are systematically consolidated from literature and published in the Malaria Threats Maps database (13). Harmonized protocols and a dashboard for planned and ongoing studies have been published and a laboratory network has been established.
- **Objective 2:** Provide concrete guidance to countries on malaria diagnosis and treatment in settings where such mutations are found to be frequent. Guidance is available in the response plan and an update based on lessons learned is planned. The plan is to update the *pfhrp2/3* response plan to incorporate lessons learned from countries that have changed their policy. Review recent literature and surveillance data to compare the performance/sensitivity of HRP2 and pf-LDH RDTs in order to inform “switch criteria” and track research on the evolution and spread of *pfhrp2/3* deletions in parasite populations.
- **Objective 3:** Identify gaps in knowledge on the genesis and spread of strains with *pfhrp2* and/or *pfhrp3* deletions and the actions required to develop new, accurate tests for malaria based on alternative target antigens. Work is ongoing to track research on the evolution and spread of *pfhrp2/3* deletions in parasite populations. Emerging genetic analysis excludes distant importation from South America to Africa and supports separate deletion events and increase in proportion of *pfhrp2*-deleted parasites untreated because of false negative HRP2 RDTs and more distant *pfhrp3* deletions. While there are pf-LDH RDTs in the WHO prequalification pipeline and additional tests in field trials, the future may be two suppliers, which could pose supply risks. A risk-based transition plan and forecast for pf-LDH RDTs over the next five years, identifying the highest risk countries, prioritizing surveillance and a plan to switch tests, is necessary.
- **Objective 4:** Coordinate advocacy and communication with donors, policy-makers, test developers, research agencies, technical partners and disease control programmes to assist in planning. Data-driven policy changes were supported in Djibouti, Eritrea and Ethiopia, and there is a call to incorporate

molecular surveillance efforts in the *Strategy to respond to antimalarial drug resistance in Africa*. The Malaria Threats Maps dashboard will give donors, policy-makers, programme managers and manufacturers better visibility on planned and ongoing studies.

The Global Malaria Programme welcomed feedback from MPAG on current and planned activities, prioritization of outstanding questions and advice on focusing efforts to best coordinate with partners to minimize negative impacts, optimize continued use of HRP2 RDTs and maintain healthy RDT markets.

**MPAG conclusions:** MPAG congratulated the Global Malaria Programme on the progress over the last six months in standardizing *pfhrp2/3* deletion detection and on work to modify and update the Malaria Threats Map. MPAG recognized that the extent of *pfhrp2/3* gene deletions throughout Africa is not fully understood because of the limited sampling in many regions. Efforts to expand molecular surveillance in Africa should facilitate the development of a more comprehensive picture, and WHO should work closely with other stakeholders to make this a clear use case. Global funders should consider additional emphasis on supporting malaria genomic surveillance because of the increased importance for national malaria programmes.

Questions were raised about cross-reactivity with *pfhrp2* and *pfhrp3* in current RDTs and variation in the level of cross-reactivity with some manufacturers' brands. A second question was raised about potential diversity in the pf-LDH antigen affecting RDT performance and it was suggested to monitor the potential impact as pf-LDH tests are rolled out. A point was raised about the impact of misdiagnoses, either through the deletion of the target antigen or reduced detection levels of the pf-LDH tests, including the impact on malaria case management and malaria morbidity and mortality. Such information could help WHO to refine the recommended 5% cut-off point for switching to an alternative RDT. Moreover, it was suggested that the change of diagnostic test by countries should be guided not only by clinical data but also by cost-benefit analysis. It was also emphasized that the calculation of the threshold for change is based on HRP2 RDT failure due to *pfhrp2* deletions among suspected malaria cases presenting at health facilities, not on the prevalence of *pfhrp2* deletions in the general population. The determination of the threshold should always be based on standardized WHO methodology.<sup>1</sup> The discussion highlighted the need for additional suppliers of quality-assured pf-LDH RDTs. Having a single or small number of manufacturers with a prequalified product is a great risk in terms of both pricing and supply. A main obstacle to further test development is the lack of incentive for manufacturers, and MPAG encouraged WHO to explore strategies such as advance market commitments or the United States Federal Drug Administration schemes for neglected tropical diseases and orphan products. This has been an ongoing challenge, but the current threat warrants a redoubling of efforts. Donors are strongly urged to invest in assuring an adequate supply of appropriate RDTs and in finding innovative ways to facilitate the development of new RDT products as needs are identified.

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1. Proportion of *P. falciparum* cases with false-negative HRP2 RDT results due to *pfhrp2/3* deletions = 
$$\frac{\text{\# of confirmed } P. falciparum \text{ patients with } pfhrp2/3 \text{ gene deletions and HRP2 RDT negative results}}{\text{\# of confirmed } P. falciparum \text{ cases (by either RDT or microscopy)}}$$

## Update on the spread of *An. stephensi* in Africa and the WHO response

**Background:** *An. stephensi* is a major malaria vector from south Asia first reported in Africa in 2012. *An. stephensi* is flexible in its larval site choice and is especially able to use urban larval sites. Furthermore, it is resistant to many insecticides used for public health. Despite its preference for cattle or goats, in the absence of these animals in urban settings, it bites humans infected with malaria and is a good vector for both *P. falciparum* and *P. vivax*. WHO has included the monitoring of invasive species in its Malaria Threats Map to help track the spread of *An. stephensi*, indicating both native and invasive occurrences. Mapping of negative findings will soon be added to complete reporting. The Global Malaria Programme is working to understand the impact of *An. stephensi* through epidemiological monitoring, as well as through modelling studies. Two examples of epidemiological impact include the increase in cases in Djibouti from 27 cases in 2012 to over 73 500 cases in 2020, and a case control study during the dry season in Dire Dawa, Ethiopia in 2022. Models developed to understand the spread and impact of *An. stephensi* indicate that the spread of *An. stephensi* to suitable areas in Africa could result in increased risk for up to 126 million people. Similarly, *An. stephensi* in Ethiopia could result in a 50% increase in cases (although it should be noted that there are extremely wide confidence intervals for this estimate).

To facilitate the development of a coordinated response to the spread of *An. stephensi* in Africa, an initiative was recently launched with five key aims: facilitating information exchange, increasing collaboration, strengthening surveillance, prioritizing research and developing guidance. Information exchange is critical to ensure that information is shared between researchers and countries, particularly between areas where *An. stephensi* is native and areas where it is invasive. This information exchange can lead to increased collaboration on monitoring strategies, policy development and other areas. Surveillance must be strengthened, not only entomological surveillance to understand the spread and bionomics, but also epidemiological surveillance to see where malaria is increasing or decreasing. As there is still a lot to learn about the biology and control of *An. stephensi*, research to develop new tools to control it efficiently may need to be prioritized as part of scaling up a response to attempt further spread of the vector. Finally, as the evidence-base on *An. stephensi* is strengthened WHO guidance will be evolved to refine the response. It will be important to mount an appropriate response; given resource constraints there is a risk that important work in this area may not be funded or may be funded at the expense of maintaining control of the native malaria vectors in Africa, which is already underfunded. Key next steps will be to update the document *Vector alert: Anopheles stephensi invasion and spread: Horn of Africa, the Republic of the Sudan and surrounding geographical areas, and Sri Lanka: information note (14)*, originally published in 2019, and to convene partners in Ethiopia in March 2023.

**MPAG conclusions:** MPAG recognized the progress made by the Global Malaria Programme in efforts to address the invasion of *An. stephensi*. In particular, MPAG was pleased to see a more considered approach that recognizes the risk of not paying sufficient attention to the problem as well as the risk associated with paying too much attention to it. It was noted that the response to *An. stephensi* should be backed by field data on the basic biology of the vector, the extent of its spread and its contribution to malaria transmission in different settings. MPAG suggested that WHO should continue to pay special attention to Eastern Africa where *An. stephensi* is geographically coincident with other biological threats to malaria (i.e. drug resistance, insecticide resistance, *pfhrp2/3* mutations) (13).

Additional comments and suggestions made by MPAG were as follows.

- There is inadequate vector surveillance for all vectors and this needs to be strengthened regardless of the prevalence of *An. stephensi*.
- MPAG noted the references to local elimination of *An. stephensi*, drawing lessons from the elimination of *An. gambiae* from Brazil in the 1940s (15). This assessment would require comprehensive data on the biology and spread of this species. An evaluation of control strategies within the endemic range of *An. stephensi* should be carried out.
- It is important to integrate *An. stephensi* control with the surveillance and control of other vector-borne diseases, particularly in urban landscapes. Such integration will require significant investments in capacity-building.
- MPAG queried how much is known about *An. stephensi* (e.g. its basic biology and ecology, its contribution to malaria transmission in different settings) and other container-breeding vectors such as *Aedes aegypti* in Africa.
- Regarding the data presented from Djibouti, MPAG recommended that further analysis be done of those data (and similar data sets from other countries) to ascertain whether the rise in cases can be fully attributed to *An. stephensi* and to understand what else could be happening in such settings.
- MPAG noted that efforts targeting *An. stephensi* should be integrated into broader vector control programmes and that countries should resist the temptation to treat *An. stephensi* as a stand-alone challenge (16). Control measures should involve commensurate efforts against other important malaria vector species and also non-malaria vectors such as *Ae. aegypti*, which shares aquatic habitats with *An. stephensi* in urban settings.
- Lastly, MPAG suggested that effective surveillance and control of *An. stephensi* should be incorporated into the *Global framework for the response to malaria in urban areas*.

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All documentation related to this meeting can be found at: <https://www.who.int/news-room/events/detail/2022/10/11/default-calendar/22nd-meeting-of-the-malaria-policy-advisory-group>

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