

WHO Malaria Policy Advisory Group (MPAG) meeting

APRIL 2021

MEETING REPORT

SUMMARY

On 13–15 April 2021, the World Health Organization (WHO) Malaria Policy Advisory Group (MPAG) convened virtually to review updates and progress, and to provide guidance on thematic areas of work by the Global Malaria Programme (GMP).

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

The key conclusions of MPAG to GMP included:

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

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

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

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

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

BACKGROUND

The World Health Organization (WHO) Global Malaria Programme (GMP) convened the Malaria Policy Advisory Group (MPAG) for its 19th meeting via a virtual platform on 13–14 April 2021. MPAG generally convenes twice annually to provide independent strategic advice to WHO on technical issues related to malaria control and elimination. Over the course of the two-day meeting, 17 MPAG members, national malaria programme (NMP) managers, the WHO Secretariat, and over 200 active observers (of 473 registered) discussed updates and progress in the work areas presented. The Group discussed conclusions and recommendations to GMP in a closed session on day three.

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

UPDATES FROM THE GLOBAL MALARIA PROGRAMME

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

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

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

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

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

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

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

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

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

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

SUMMARY OF THE MPAG SESSIONS

Rethinking Malaria

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

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

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

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

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

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

MPAG responded to the three major foci of this work:

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

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

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

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

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

Conclusions from the recent analysis of quality datasets from a range of transmission settings in sub-Saharan Africa in different time periods and age groups indicate that, according to the model, using parasite density cut-offs of 100 p/μL or 200 p/μL does not significantly affect the ability to detect clinical malaria and that improvements in sensitivity are coupled with reductions in specificity and poorer positive predictive value (PPV) – negative predictive value is very high. Furthermore, more sensitive tests may overestimate the true burden and have implications for burden of disease estimates. In addition, more sensitive tests/lower cut-off specifications may well detect more malaria infections, but not malaria disease. This indicates the need to always include an assessment for non-malaria causes of fever, as the PPV is not good even when using cut-offs <400 p/μL. Please refer to the accompanying slide presentation for more details on the methodology and data used in the analysis.

MPAG conclusions: MPAG noted that the analysis on parasite density and clinical malaria included nine datasets, all of them from sub-Saharan Africa. According to the model, using a parasite density of 100 p/μL or 200 p/μL does not significantly affect the ability to detect clinical malaria cases. In other words, the currently available tests, which have a detection threshold around 200 p/μL, do not miss many clinical malaria cases in sub-Saharan Africa. The analysis did not consider seasonality or intensity of transmission, but the attributable fraction should address these factors. The Group felt that it was unlikely that these factors would change the results of the analysis. MPAG noted that the relationship between *pfhrp2* blood levels and parasite density is not linear, but the relationship between pLDH blood level and parasite density may be more linear; it recommended efforts to better characterize this relationship.

The analysis did not consider the clinical consequences of untreated “asymptomatic” low density infections missed by routine microscopy and RDTs and some members raised concern that these infections may not be benign and treatment, particularly in patients attending clinics, may yield clinical benefits. Therefore, it was agreed that MPAG would encourage a review of this topic and research to better understand the clinical consequences of missed low-density malaria infections.

The overall consensus of MPAG was that it is reassuring that the minimum sensitivity requirements of currently available RDTs and microscopy are sufficient to capture clinical malaria in endemic areas of sub-Saharan Africa. MPAG also noted that other causes of fever should always be actively investigated, even if microscopy or the RDT is positive, because in all datasets the PPV was high only when the parasitaemia thresholds were several fold higher than the limits of detection of current tests. MPAG reinforced the need to ensure that recommendations for case management and training and supervision of health care providers adequately emphasizes this point to guarantee that health care providers consider, and look for other causes of fever, even in case of positive malaria RDT or microscopy. MPAG therefore encourages a review and additional implementation research to generate evidence of the clinical and public health benefits of identifying and treating patients with lower density infections attending clinical facilities. Given the lower intensity of transmission outside sub-Saharan Africa, results may be different. Therefore, MPAG recommends that a similar analysis be undertaken outside sub-Saharan Africa for *P. falciparum* and *P. vivax*.

Update on the situation of antimalarial drug efficacy and resistance in Africa

Background: To respond to malaria drug resistance, systems are needed that detect changes in how well the recommended treatment is working and that can implement changes in treatment policy when indicated. Therapeutic efficacy studies (TES) are the gold standard for monitoring drug efficacy to inform treatment policy; in elimination settings, efficacy can be monitored using integrated drug efficacy surveillance (iDES). In vitro and ex vivo studies and surveillance of molecular markers indicating genetic changes associated with resistance provide additional information. Once genetic changes associated with resistance are identified, drug resistance can be confirmed with molecular techniques. Resistance in *P. falciparum* has posed the greatest challenge for the artemisinin-based combination therapies (ACTs) recommended for the treatment of uncomplicated *P. falciparum* malaria. Efficacy of partner drugs should also be considered and assessed. In most of the world, these antimalarial drugs are highly efficacious, although resistance in the Greater Mekong Subregion (GMS) does pose a challenge.

A Report on antimalarial drug efficacy, resistance and response: 10 years of surveillance (2010–2019) was published in November 2020. The report draws on data collected through more than 1000 TES as well as molecular marker studies of *P. falciparum* drug resistance to present a decade’s worth of data and recommendations to monitor and

protect the efficacy of malaria treatment. During this period, 650 TES were conducted in Africa using six different ACTs. Nine out of 323 studies using artemether-lumefantrine in Africa found >10% failure rate; later studies in the same area as five older studies found <10% failure rate; and four recent studies need confirmation. Two out of 70 studies using dihydroartemisinin-piperaquine in Africa found >10% failure rate. *PfK13* mutations have been identified as a marker of resistance to artemisinin and its derivatives and is associated with delayed parasite clearance. Four countries in Africa have reported less than 95% *PfK13* wild type: Eritrea, Rwanda, Uganda and Ghana. All data on malaria drug efficacy and resistance are available on the WHO Malaria Threats Map.

WHO published guidance on genotyping to identify parasite populations for clinical trials in 2008, and a review was undertaken by a Technical Expert Group on drug resistance in 2017. Recent publications have triggered the need to review new methodologies, and an informal consultation will be convened to update the methodologies to distinguish reinfection from recrudescence in high malaria transmission areas. The consultation objectives are to: 1) review data and assess the advantages and disadvantages of changes to the markers used to differentiate recrudescence from reinfections and changes to the algorithms used to classify recrudescence and reinfections; 2) assess in which transmission settings a change to the current methodology could improve the precision of the classification of recurrent *P. falciparum* as recrudescence or reinfection; and 3) discuss potential alternative tools for use in the future and suggest research needed to validate these tools.

MPAG conclusions: MPAG members appreciated the presentation and agreed with the conclusions on the need for continued surveillance outside the GMS, and the need to validate mutants and to monitor worldwide artemisinin resistance. The Group supported the convening of the informal consultation to provide advice to WHO.

MPAG emphasized the need to actively conduct surveillance on ACT efficacy and resistance and noted that, based on the data, most of the reported cases appear to be late resistance due to the failure of and resistance to the partner drug. This finding is an issue due to the potential for transmissibility, which is an important problem particularly in elimination settings. MPAG strongly endorsed the proposed activities to minimize the risk of emergence and spread of resistance. These include preventing resistance; monitoring drug efficacy and resistance; responding to drug resistance deemed to be a potential threat to public health; delivering quality services and targeting of activities; and developing the tools, knowledge and evidence base. MPAG re-emphasized the need to follow the current WHO recommendation to treat uncomplicated malaria with an approved ACT and that a complete ACT treatment should be administered following the use of intravenous or intramuscular artesunate or rectal artesunate for severe malaria.

MPAG further recommended that efficacy and resistance studies should use standard methodology to ensure comparability and high-quality results, and highlighted the need to validate mutations with clinical response. There is a need to formulate a strategy on how to respond quickly based on data, how to identify the best second-line treatment when the first-line treatment is failing, and how to support countries and partners to implement activities to prevent emergence and spread of resistance. MPAG also noted the need to build capacity for ex vivo and in vitro studies to monitor drug sensitivity of the parasite populations.

Proposed technical consultation to stage *P. knowlesi* along the continuum between zoonosis and human pathogen

Background: *P. knowlesi* is a zoonotic malaria parasite species transmitted between non-human primate hosts that frequently spills over into the human population in areas where the parasite, vector, primate host and humans converge. Most countries in South-East Asia have reported *P. knowlesi* infections in humans and Malaysia has now eliminated all other malaria species that infect humans. However, since 2009, when Malaysia began retesting all samples identified as *P. malariae* using PCR, the country has reported between 300 and 4000 cases of *P. knowlesi* each year.

Emerging zoonotic infections are classified into five stages based on epidemiological dynamics in the incidental host: Stage 1 – agent only in animals; Stage 2 – primarily animal infection; Stage 3 – limited outbreaks in humans; Stage 4 – sustained humans-mosquito-human transmissions; and Stage 5 – exclusively human agent. Pathogens in Stages 1–2 are not considered to be human infections, but Stage 4 and 5 are considered to be human pathogens, with critical implications for human malaria elimination and eradication. For example, yellow fever, a Stage 4a pathogen, was considered for eradication during the first decades of the 20th century. However, when the importance of the sylvatic reservoir was identified, it was determined that eradication was not feasible. The implications for eradication of the classification of zoonotic pathogens as Stage 3 are less clear. Stage 3 is characterized by stuttering chains of human cases because the pathogen is weakly transmissible between humans ($R_0 < 1$). Stage 3 pathogens have caused outbreaks and limited human-to-human transmission that ultimately die out or are controlled. Stage 4 have long sequences of transmission between humans without involvement of animal hosts ($R_0 > 1$). This stage has been further divided based on the relative importance of transmission within the reservoir or incidental host:

- Stage 4a: The sylvatic cycle is much more important than direct human-to-human spread, e.g., Chagas disease and yellow fever.
- Stage 4b: Both the sylvatic cycle and human-to-human transmission are important, e.g., dengue fever in some forested areas of West Africa and South-East Asia.
- Stage 4c: Transmission between humans is more important, e.g., influenza A, cholera, typhus, SARS-CoV2.

A 2017 WHO Evidence Review Group (ERG) examined the available evidence to consider whether sustained human-mosquito-human transmission of *P. knowlesi* was occurring. The ERG concluded that *P. knowlesi* remained primarily a zoonotic infection (i.e., Stage 2), but stressed the need to further investigate the possibility of human-mosquito-human transmission. If there is evidence that *P. knowlesi* is a Stage 3 or 4 pathogen, the criteria for the certification of malaria elimination may need to be revisited. The objectives of the technical consultation are to:

1. Review the evidence from a systematic review of the literature on *P. knowlesi* to determine whether human-mosquito-human transmission is occurring and whether sustained transmission is possible.
2. Review the results of spatiotemporal analysis of *P. knowlesi* case data from Malaysia that attempt to identify clusters of cases that could have arisen from human-mosquito-human transmission.
3. Recommend to WHO a current staging of *P. knowlesi* on the zoonotic continuum based on the evidence reviewed.

4. Outline a research and surveillance plan to monitor for emergent changes in the human transmission potential of *P. knowlesi*.

According to WHO, certification of malaria elimination requires the interruption of local transmission for all human malaria parasites, which have been defined as *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*. Reclassification of *P. knowlesi* as a human malaria parasite would impact the prospects of certification of malaria elimination in all countries of the GMS, Indonesia and Malaysia. Additionally, inclusion of *P. knowlesi* as a human malaria parasite calls into question the potential for eradication of malaria, as it is generally held that pathogens that have a zoonotic reservoir cannot be eradicated.

MPAG conclusions: MPAG supported the proposed technical consultation and noted that the key question is whether there are sustained chains of *P. knowlesi* transmission events that do not involve primates, and whether this requires reclassification of *P. knowlesi* as a human malaria parasite. MPAG recognized that the results of the technical consultation could have significant ramifications for the malaria community and could require extensive consultation and discussion to reconcile or redefine the concepts of certification and eradication. MPAG noted that even if the technical consultation does not recommend reclassification of *P. knowlesi*, both *P. knowlesi* and other simian malaria parasites cause malaria disease in humans that is clinically indistinguishable from the disease caused by the four human malaria parasites, and public communication on the implications for certification of elimination should be considered independent of the staging of *P. knowlesi*.

MPAG suggested that the systematic review team ensure genomic data are well reviewed to glean insights into transmission chains and requested that the technical consultation consider the need and feasibility of conducting more in-depth prospective epidemiological and genomic investigations to find clear evidence for or against sustained human–vector–human transmission. The Group recommended that the ongoing review and any proposed epidemiological surveys attempt to establish which vector species are involved in transmission at different stages (animal–mosquito–human vs. human–mosquito–human).

MPAG congratulated the Malaysian government for its development of a *P. knowlesi* control strategy and emphasized the importance of prioritizing *P. knowlesi* cases for case management and control in the other countries reporting *P. knowlesi* cases in the region.

Update on the threat of *pfhrp2/3* deletions in the Horn of Africa region

Background: RDTs target a range of malaria antigens for detection, including histidine rich protein-2 (HRP2), parasite lactate dehydrogenase (pLDH) and aldolase; the majority of RDTs used to detect *P. falciparum* target HRP2. The first reports of *pfhrp2/3* deletions were in 2010 in Peru, and by 2016, there was a turning point with a very high prevalence of double deletions in Eritrea and low but heterogeneous prevalence of deletions in India. WHO published a *Response plan to pfhrp2/3 gene deletions* in 2019 and *Template protocols to support surveillance and research for pfhrp2/3 gene deletions* in 2017 and 2020. The response plan called for four key responses against which substantial progress has been made for all but the first, which requires further action from countries and their global partners: 1) mapping the distribution and frequency of *pfhrp2/3* deletion mutants with harmonized protocols; 2) building an international network of laboratories to perform the complex molecular confirmation required for mapping and identifying new and/or efficient screening methods; 3) supporting countries in the selection and procurement of new RDTs when a change of testing is warranted; and 4) advising commercial manufacturers on the priorities for new tests and providing the best available market forecasts.

The criterion signalling the need to change the RDT in use is if a survey confirms that the presence of *pfhrp2/3* deletions causing false-negative HRP2 RDTs is greater than 5%. In this case, the NMP needs to take a series of actions to immediately optimize case management and plan for the introduction of replacement RDTs. The change should be applied nationwide, although the roll-out might be prioritized based on the prevalence of *pfhrp2/3* deletions in different regions. The Malaria Threats Map tracks the data in published reports, which is typically a percentage of *pfhrp2/3*-deleted samples among those tested (not all *P. falciparum* cases). Reported data are from different populations (age, symptoms/no symptoms, selection criteria for genotyping) and the RDT result is not always known; therefore, original source data are required to properly interpret the results.

Many countries want to conduct surveys, but lack funding. WHO convened a workshop in 2019 with five countries in sub-Saharan Africa to develop country-specific protocols and budgets. To date, only the United Republic of Tanzania has funding and others are awaiting the outcome of grant applications. Several countries in the Horn of Africa Region including Ethiopia accumulated evidence of have indisputably high prevalence of *pfhrp2* deletions, including dual deletions of *pfhrp2* and *pfhrp3*. Eritrea and Djibouti have changed RDTs to pan-LDH and pf-LDH platforms based on WHO guidance and on findings in a limited geographical area. Ethiopia received signals of a problem based on high prevalence of discordant RDTs in 2018. In 2021, however, the country is still using PfHRP2/Pv-LDH combo tests, which have 0% detection of dual deletion of *pfhrp2* and *pfhrp3* parasites. With continued HRP2 RDT pressure, the problem is anticipated to worsen, and follow-up data from Eritrea and Peru illustrate that *pfhrp2/3* deletions can persist after HRP2 RDT pressure is removed entirely (or where it has not been substantially applied); this suggests that other factors are at play. An alternative combination test that does not rely on PfHRP2 is available and in the WHO prequalification (PQ) pipeline and approved by the Global Fund Expert Review Panel for Diagnostics (ERPD).

MPAG conclusions: MPAG noted that the issue of HRP2 gene deletions has emerged as a threat that requires urgent attention, as it has the potential to derail the gains made in reducing malaria mortality. MPAG felt that the inability to detect *falciparum* malaria cases may result in progression to severe disease and death, as well as an erosion of confidence in malaria RDTs. The Group congratulated the Secretariat for taking pre-emptive steps to develop a Global Response Plan, including establishing a network of laboratories to carry out the assessments, supporting the development of national protocols, and identifying the criterion to indicate a change of the RDTs in use. MPAG expressed concern over the lack of resources to enable countries that have picked up signals of *pfhrp2/3* deletions to map their distribution and frequency in order to assess the magnitude of the problem. The Group noted that lessons could be learned in communication, implementation and decision making from the switch from chloroquine to ACTs.

MPAG further noted that innovative ways must be found to provide the needed resources to this urgent problem. Some proposals involved encouraging countries to include surveys in their Global Fund grants; another proposal suggested integration into routine TES monitoring. MPAG noted that while some TES sites may be suitable for detecting signals of a potential problem, this approach alone will not suffice for estimating the prevalence of deletions without information from cross-sectional surveys. MPAG proposed that the Secretariat leverage existing regional malaria networks, such as the Horn of Africa Network for Monitoring Antimalarial Treatment (HANMAT), to ensure that the issue of *pfhrp2/3* deletions is a priority on their agenda.

MPAG emphasized the need for research and development of improved non-HRP2-based RDTs and welcomed the news that one combination test detecting *P. falciparum* through a species-specific LDH has entered the PQ pipeline and obtained ERPD approval for Global Fund procurement. Information was provided that two or three other

manufacturers are developing non-HRP2-based RDTs with a target limit of detection to detect clinical malaria. Some products are advancing well, although there is some concern about stability at higher temperatures. MPAG considered whether the WHO Emergency Use Listing (EUL) process or designation as a public health emergency of international concern (PHEIC) should be invoked to speed the approval and availability of new products. MPAG concluded that a strong statement stressing the urgency of the current situation would be an appropriate next step.

The Group also identified the need for research on the drivers of emergence and selection for *pfhrp2/3*-deleted parasites as a priority to guide efforts to combat their expansion. It was noted that mathematical models strongly suggest that a reliance on HRP2-based diagnostics will continue to select for deleted parasites, but more genetic analysis is required to understand the emergence and spread of parasite strains carrying the deletions. MPAG further noted that *pfhrp2* deletions have also spread throughout South America, despite very infrequent use of RDTs for malaria diagnosis, as most countries rely heavily on microscopy.

MPAG noted with concern the reluctance of some countries to switch to non-HRP2-based RDTs, despite undisputedly high prevalence of *pfhrp2* gene deletions that surpasses the WHO-recommended criterion for change. MPAG emphasized that in the context of continued expansion of the deletions, including into the Horn of Africa, it is imperative for countries, including Ethiopia, to urgently respond to this immediate threat to malaria diagnosis and treatment for communities in the Region and the broader threat to human life and malaria elimination in sub-Saharan Africa. MPAG urged affected countries to take urgent action and resolved to issue a statement to encourage such action. The statement will call attention to the urgency of responding to *pfhrp2/3* deletions as an emergent threat with life-threatening potential. The statement will restate the recommended criterion for changing to non-HRP2-based diagnosis of *P. falciparum*, and emphasize that countries should take action on the basis of the best available data they have, consider a nationwide policy change even if representative data are limited to one or more subnational areas, and share information to coordinate diagnostic policy decisions with neighbouring countries.

Proposed technical consultation on the response to malaria in urban areas

Background: In the period 2000 to 2030, the world's urban population is expected to increase from 2.7 billion to 5.1 billion, accounting for 60% of the total population. WHO's SAGme report identified rapid urban population growth as one of the key megatrends influencing the vision of a malaria-free world.

Among the fastest growing regions is sub-Saharan Africa, which also accounts for over 94% of the current global burden of malaria. In this region, the proportion of the population living in urban areas increased from 31% (457 million) to 47% (680 million) between 2000 and 2020. By 2050, 58% of the population in sub-Saharan Africa will be urban. In the HBHI countries in Africa, 43% of the population is already in urban areas, but there are no clear approaches to targeting malaria interventions in urban areas. The urban malaria problem is not a medium- to long-term concern, but one that needs urgent attention now. Well-planned urbanization is expected to help 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 may come with 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 *Anopheles gambiae* s.l. to polluted waters. The invasion by *An. stephensi*, which is highly

adapted to the urban environment is an emerging challenge in sub-Saharan Africa. High-volume, short-term and seasonal human population movements into urban areas mean that a substantial proportion of malaria in urban areas is imported. In urban areas, a large fraction of the population seeks malaria treatment in the private sector, potentially receiving substandard care, especially in the uncontrolled informal sector.

WHO does not currently have recommendations and implementation guidance specific to urban malaria. The majority of the evidence underpinning current WHO malaria prevention recommendations relies on efficacy data from rural malaria-endemic settings. Consequently, most countries implement similar interventions in both urban and rural settings, despite important differences in the transmission dynamics and environmental, behavioural, socioeconomic and care-seeking determinants. ITNs, for example, are still widely distributed in African cities, despite little evidence of their efficacy and effectiveness in urban areas, and some data show that use among those who own nets is often lower in urban areas than in rural ones. Clear guidance on malaria control in an increasingly complex urban health dynamic is urgently needed.

GMP will convene a technical consultation to develop a WHO framework for the response to malaria in urban areas in order to address the increasing urban population growth and evolving malaria transmission dynamics in malaria-endemic countries. The objectives of the technical consultation are to:

1. document the current practices and lessons learned in the response to urban malaria across WHO regions;
2. identify effective interventions suitable for reducing the malaria burden and eliminating it in urban settings;
3. propose methods for urban malaria risk characterization and microstratification to inform targeting of the malaria response; and
4. define urban malaria research priorities and explore issues related to study designs.

MPAG conclusions: MPAG congratulated WHO for the initiative to convene a technical consultation on the burden and response to malaria in urban areas and agreed that this was a timely and very necessary activity. MPAG noted that the materials focused on sub-Saharan Africa, but it was clarified that the geographical scope of the consultation will be global and will include experts from all Regions.

The discussion and recommendations focused on six main issues:

1. **Health services:** MPAG noted that it will be important to recognize the heterogeneity in access to health services within urban spaces, which will be key to understanding accessibility and potential effects on drivers and patterns of disease; and the issue of service providers' recognition of clinical malaria in areas where malaria is not a common disease, potentially leading to undiagnosed and untreated disease.
2. **Movement patterns:** MPAG supported the need to differentiate between the place of infection and place of diagnosis in order to define effective control strategies. It was noted that there are many countries in Latin and South America that do not collect this information in their routine malaria health system.
3. **Vector considerations:** MPAG highlighted that urban strategies will also depend on the vector species' potential to adapt to pollution in cities, and should consider lessons learned from dengue control and what is known about effective integrated

vector management (IVM) strategies. The Group emphasized the importance of making micro-stratification approaches, IVM, continuous monitoring, and a multisectoral approach central topics of discussion in the consultation.

4. **Lessons learned:** MPAG suggested drawing on historical experiences where malaria control has been successful in urban environments, including places where those efforts later broke down (particularly in India), and looking at the control of other urban disease programmes (e.g., dengue or tuberculosis).
5. **Alignment with other new initiatives:** MPAG noted that the “Rethinking Malaria” consultation process will help inform how best to engage communities and stakeholders in the implementation of urban malaria control strategies and encouraged alignment between the two areas of work. MPAG highlighted the need to consider how the urban malaria consultation will align with the idea of going to the ‘last mile’ and reaching the ‘most vulnerable’. Additional questions the Group posed for consideration were: Are those ‘most vulnerable’ to malaria in urban areas or in remote rural areas, and what are the relative costs of addressing malaria in this urban population compared to the ‘last-mile’ vulnerable populations in rural areas where malaria mortality is highest?

Update on management of severe malaria

Background: Severe malaria is defined by clinical and laboratory evidence of vital organ dysfunction and is mostly caused by *P. falciparum*; however, *P. vivax* and *P. knowlesi* can also cause severe disease. The risk population varies by transmission area; in high-transmission areas, young children and travellers from non-endemic areas are at highest risk, while in other transmission areas, all age groups are at risk. The therapeutic objectives are, first, to prevent the patient from dying and, second, to prevent disabilities and recrudescence. Severe malaria is a medical emergency that requires rapid diagnosis and the initiation of treatment as soon as possible at the highest possible level of care. The areas of potential intervention to prevent malaria progression and death include vector control to prevent inoculation, chemoprevention to treat asymptomatic infection, and early diagnosis and treatment of uncomplicated malaria before it reaches severe malaria and potentially death. Management of severe malaria comprises four main areas: clinical assessment of the patient, specific antimalarial treatment, additional treatments to manage other complications, and supportive care.

The current norms and standards available to guide the management of severe malaria are included in three publications: The recently consolidated *WHO Guidelines for malaria*, the *Management of severe malaria: a practical handbook* (3rd edition, 2013) and the Severe Malaria Supplement in the *European Journal of Tropical Medicine & International Health* (2014). The target audience of the WHO Guidelines is policy-makers to guide the development of national treatment policy and guidelines, not intended to be used as a manual or treatment handbook for health professionals. The Practical handbook focuses on the practical management of severe malaria and is intended for health professionals working in hospitals or health centres with in-patient facilities, who are responsible for the management of severe malaria patients. It covers all aspects of management – from triage to diagnosis and treatment, nursing care, follow-up and post-treatment rehabilitation. Finally, the Supplement provides a series of literature reviews and consensus opinions from a WHO consultation in 2011, covering aspects of severe malaria, including epidemiology, definitions, clinical disease in different groups, pathophysiology, pathology, management and pharmacology of antimalarial medicines.

Several implementation challenges at country level have been identified, including suboptimal uptake of WHO Guidelines at the national level, weaknesses of the health system such as medication availability and referral systems, capacity of the health

work force where training and training updates are important, quality of care and the continued use of monotherapy. Going forward, the recommendations on the management of severe malaria remain current, as there are presently no indications or evidence to propose updated recommendations. However, the Practical handbook requires an update to align with the current recommendations. Updates include the preference in the order of antimalarial choices for the treatment of severe malaria, recommendations on dosage adjustment in children, and a review of fluid management and other supportive treatment. In addition, updated implementation guidance for the effective deployment of rectal artesunate by community health workers will be developed in the coming months, following the completion and assessment of evidence from the Unitaid-funded CARAMAL project. WHO will continue to provide implementation and country support to update national policies and build the required systems and capacity to effectively manage severe febrile illness including severe malaria.

MPAG conclusions: MPAG endorsed the proposed plan to update the *Management of severe malaria: a practical handbook* and to develop operational guidance for the use of rectal artesunate, with an emphasis on the need for follow-up combination therapy and noting the need for enhanced country support and human capacity development. MPAG raised specific issues that should be considered in updating the guidance for the management of severe malaria: 1) recognition of the need for national policy based on the global *Guidelines for malaria*; 2) guidance on approaches to work with private practitioners; 3) the need to better communicate with caretakers and patients on the importance of timely care-seeking from a qualified care provider and adherence to the recommendations of service providers concerning malaria case management from diagnosis to cure; 4) the importance of clear guidance for post-discharge treatment and follow-up, noting public health follow-up in areas of elimination; 5) use of an episode of severe malaria to emphasize personal protection and prevention with vector control; 6) investigation of issues linked to quality of care for severe malaria where case-fatality rates indicate a signal; and 7) consideration of the approach to severe vivax malaria.

MPAG supported the plans for implementation and country support to update national policies and build the required systems and capacity to effectively manage severe febrile illness, including severe malaria. This should involve reviewing national training curricula, identifying innovative mechanisms for training support, strengthening referral systems and keeping malaria mortality on the political agenda. The Group asked that WHO provide clarity on how it will support countries to develop the required local expertise and noted that while WHO can provide guidelines, uptake and implementation also depend on the strength of health systems and work force capacity. MPAG emphasized the importance of pre-service and in-service training for all providers involved in the management of severe malaria, including those in the private sector, from first presentation to in-hospital care, which should be considered in the context of UHC.

Update on work related to implementing a revised classification of ITN products

Background: May 2020, the classification of ITNs was revised into three classes summarized here:

1. ITNs designed to kill host-seeking insecticide-susceptible mosquito populations that have demonstrated public health value compared to untreated nets and whose entomological effects consist of killing and reducing the blood-feeding of insecticide-susceptible mosquito vectors.
2. ITNs designed to kill host-seeking insecticide-resistant mosquitoes for which a first-in-class product has demonstrated public health value compared to the epidemiological impact of pyrethroid-only nets.

3. ITNs designed to sterilize and/or reduce the fecundity of host-seeking insecticide-resistant mosquitoes for which a first-in-class product has demonstrated public health value compared to the epidemiological impact of pyrethroid-only nets.

The adoption of the revised classification was made conditional on a number of areas being addressed by WHO: 1) update of WHO documentation on the evaluation process to reflect changes made to the ITN classification and evaluation; 2) identification and closure of existing data gaps on new types of nets currently prequalified (including pyrethroid+PBO nets); 3) establishment of a process within WHO to define similarities for existing and future ITN products; 4) revision of ITN testing guidelines to allow comprehensive evaluation of nets other than pyrethroid-PBO products; 5) review of the ITN classification within a period of three years to establish whether the revised classification continues to capture the available products and those under development, and whether there may be opportunities to further simplify classification; and 6) at least annual updates to MPAG on the data available to update this classification.

Significant progress has been made in the areas to be addressed. A document outlining the *Norms, standards, and processes underpinning development of WHO vector control recommendations* was published in December 2020 to reflect the changes made to ITN classification and their evaluation. This document replaces information on the vector control evaluation process published in 2017. The identification and closure of existing data gaps through epidemiological data to inform WHO recommendations is dependent on ongoing trials and will be considered when the data are available. The WHO Pre-submission Coordination Committee reviews product characteristics against established intervention classes and a non-inferiority method is being evaluated as a potential method to assess the comparative effectiveness of products within the same intervention class. A technical consultation will be convened in September 2021 to revisit this topic, drawing on non-inferiority data from two experimental hut study trials conducted on pyrethroid-PBO nets. Requirements for the classification of ITNs for the determination of public health value have been developed; and requirements for chemistry and manufacturing data to support the quality of the product are under review. Requirements for safety, determined through an assessment of exposure data, are ongoing. The review of current data requirements to assess the impact on the vector was completed and areas for strengthening were identified and discussed by the Assessor Group. The scope of new data requirements will focus on expanding laboratory studies and semi-field studies and aligning the data that support chemistry and manufacturing requirements and efficacy requirements. Finally, the revision of the Guidelines for laboratory and field-testing of long-lasting insecticidal nets has been finalized and will be published in the PQ/Vector Control Programme (PQ/VCP) Oversight Document, Operations Manual.

MPAG conclusions: MPAG noted that the importance of ITNs to the control and elimination of malaria, coupled with the complexity of vector control, is reflected in the sustained interest in and importance of the classification of ITN products, which is reviewed annually. MPAG felt that while the present ITN classification system of three classes based on entomological effect is not perfect, it does provide a clear and needed framework for defining a first-in-class product requiring evidence of epidemiological effectiveness in two trials. MPAG strongly supported the continued investigation on the use of non-inferiority study designs to generate data to compare product performance within a class, as well as the planned technical convening in September 2021 to further assess the potential value of this approach based on two non-inferiority datasets on pyrethroid-PBO nets. MPAG recognized the significant progress that has been achieved on classification and evaluation of ITNs as a means to expedite a WHO recommendation and prequalification. MPAG requested clarification on the process to review products that have been prequalified and associated quality concerns and was assured that the PQ/VCP team undertakes investigations of underperforming products, which can result in the loss of their PQ listing.

MPAG noted Annex 3 (Overview of intervention classes for vector control) of the *Norms, standards and processes underpinning WHO vector control policy development* and recommended that it be reviewed in future discussions. MPAG made three recommendations for further consideration:

1. Given the number of ITNs and other vector control products, the classification of vector control products should be periodically reviewed.
2. The continued effectiveness of prequalified ITNs needs to be monitored, particularly following changes to the manufacturing process.
3. Country capacity to monitor vector control products needs to be strengthened.

Update on DSME surveillance

Background: Transforming the surveillance system into a key intervention is the third pillar of the GTS. As countries progress towards malaria elimination, the aim of surveillance is to detect all malaria infections; investigate every malaria case; identify the likely location of an infection to direct actions towards interrupting transmission; and ensure that each detected case is promptly treated and monitored to prevent secondary infection. An ideal surveillance information system for malaria elimination includes rapid and complete case reporting, central data storage and management, automated data analysis, and customized outputs and feedback that lead to timely and targeted responses. An optimal, fully integrated malaria information system (MIS) facilitates the collection of complete and timely data, reporting, data analysis, active follow-up, and selection of interventions to adequately address malaria transmission.

In 2015–2016, a landscape assessment was conducted by the Clinton Health Access Initiative (CHAI), in collaboration with malaria programmes in 16 countries, to assess national surveillance systems based on the minimum standards recommended by WHO. The assessment showed several shortcomings of information systems: data collection relied largely on paper forms that were prone to data entry errors, had longer timelines for reporting, and limited the collection of geospatial data at the community or health facility level. While some countries had begun to roll out digital surveillance systems, no single information system, including DHIS2, could support malaria data collection and analysis of individual cases, case investigations, focus investigations, and interventions. The assessment revealed gaps in data analytics, visualization, and the integration of different types of malaria data. Furthermore, the mobile surveillance tools often did not correspond to the operational workflows of malaria health workers, were not built appropriately for low infrastructure and low literacy settings, and were difficult to customize. Gaps were also identified in the electronic data collection and data analysis using mobile platforms: platforms were not straightforward to customize, were unable to collect data in a non-sequential way to match how data are collected in the field, and did not support complex relationships among cases, foci or other geospatial entities.

To solve these problems, the Digital Solutions for Malaria Elimination (DSME) project was initiated in 2017, as a collaboration between WHO, CHAI and other partners, to develop and deploy effective digital surveillance tools in malaria-endemic countries. The digital tools developed as part of the DSME project are aligned with WHO standards, are adaptable to meet country needs, and are either built using DHIS2 or are interoperable with DHIS2. These tools show enormous potential for improving malaria elimination activities, and initial M&E results from country pilots have demonstrated gains in user engagement and use of data. Lessons learned on strengths and challenges from pilot countries have indicated the following next steps for WHO:

- Make the DSME digital tools available to countries for adoption to augment surveillance processes in malaria elimination settings. The tools are open-source

and available for implementation, although they may need customization to ensure they are fit-for-purpose.

- Disseminate these tools through clear communication across stakeholders: Dissemination of the tools will inform WHO, national programmes, and partners on methods to augment surveillance efforts. WHO will advocate for the scale-up of digital tools as part of broader national surveillance efforts, recognizing that countries may implement elimination surveillance processes vertically.
- Work with partners and donors to support countries to adopt, use and maintain these tools: Initial adoption relied on country buy-in, operational readiness, technical capacity, and available technical infrastructure. A strong enabling environment was particularly critical to help stabilize tools during initial roll-out, encourage tool uptake over time, and support sustainability. WHO will work with partners to facilitate support for interested countries in the installation of digital tools, training capacity and maintenance of digital tools.
- Continuously monitor uptake of tools and implement any necessary improvements: New digital tools should be continuously monitored for usability, data quality, and impact on existing processes. Regular M&E of tools should be embedded in existing processes to ensure continued added value. WHO will work with relevant departments and partners to ensure regular updates of tools in country.

MPAG conclusions: congratulated the team responsible for this initiative and felt that it demonstrates a significant improvement with fit-for-purpose tools that programmes can use to support implementation of elimination activities. MPAG recommended that as part of the dissemination plan, it would be useful to provide clear information for NMPs to consider before undertaking the digital transition to these tools, including clarifying the settings in which these tools are applicable. MPAG provided more detailed suggestions in the following areas:

- **Tool selection:** MPAG emphasized the need to make the criteria and considerations for the selection of the two platforms (Open Smart Register Platform and DHIS2) clear to countries, including details on the criteria/decision/rationale. It is important to explain the use of these platforms in the context of integrating IT and health information tools across diseases and perhaps document the experience for countries to learn from.
- **Operational challenges and digital readiness:** The Group noted that in the pilot, a lack of improvements was associated with operational constraints and these are likely to be present across many countries. MPAG suggested that a description of the constraints would be useful. WHO should consider whether clear prerequisites should be explicitly defined for countries to assess before embarking on elimination activities digitally.
- **Continuous and adaptive monitoring system:** MPAG agreed with the need to ensure that a more continuous M&E system is in place so that issues are identified and addressed on a regular basis, rather than waiting for the midline or endline assessments.
- **Case notification and investigation:** MPAG agreed that one of the challenges was the lack of standardized terminology used in forms for malaria surveillance programmes, making it difficult to measure and compare indicators across countries. MPAG suggested supporting the transition to standardized indicators and definitions more broadly beyond the pilot countries.
- **Addition of entomology component:** MPAG recommended that before rolling out the tools, it is important to include an entomology component with concrete examples on how the data are captured and used. WHO clarified that a separate

entomology module is available in DHIS2 for use in all settings, and the DSME tools are interoperable with DHIS2.

- While the DSME provides a potentially useful link to record and display data, there is a critical need to support capacity to both collect data for input into the DSME and to use the data from the DSME in decision-making.

MPAG agreed with the next steps proposed to promote the uptake of digital tools together with a suitability matrix or checklist where options, prerequisites and requirements are clearly outlined so that countries embark on such transitions fully aware and able to avoid unnecessary challenges. MPAG recommended a roll-out phase that describes the scale to enable budgeting and planning and emphasizes the importance of ongoing monitoring so that issues do not emerge at midline or endline assessments that could have been resolved earlier in implementation.

High-level recommendation: MPAG emphasized the need for WHO to consider its approach to capacity building and the implementation of guidance across the range of technical areas for malaria in the context of a need for broader health systems strengthening. MPAG strongly supports the need to strengthen the collection and use of data to move beyond the one-size-fits-all approach. The use of subnational data will inform implementation plans that can be tailored to local contexts to maximize impact and lessons learned from the success of other countries can be shared. MPAG requested an agenda item dedicated to capacity building at the next MPAG meeting.

All documentation related to this meeting can be found at:
<https://www.who.int/news-room/events/detail/2021/04/13/default-calendar/19th-meeting-of-the-malaria-policy-advisory-group>

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

