

THIRD MEETING OF THE MALARIA TECHNICAL ADVISORY GROUP (MALARIA TAG) TO THE PAN AMERICAN HEALTH ORGANIZATION (PAHO)

Summary

The third meeting of the Malaria Technical Advisory Group (Malaria TAG) was convened on June 7– 8, 2017 at PAHO Headquarters in Washington DC to review the progress of key malaria efforts carried out by the Pan American Health Organization Regional Malaria Program, discuss key technical issues, and provide recommendations where appropriate.

The meeting included 9 sessions and discussed the following topics: (1) Report from the Regional Malaria Program; (2) Regional Guidance on the Implementation of G6PD testing and radical cure in *Plasmodium vivax* endemic countries; (3) Updates regarding antimalarial drug resistance surveillance in the Americas; (4) Monitoring and Evaluation Framework for the Plan of Action for Malaria Elimination; (5) Strategy for Early Detection, Treatment, and Case Investigation; (6) Strategy for reducing relapses of *P. vivax*; (7) Cross-Border Pilot Effort on Self-testing and Self-treatment for Malaria among Miners Across the Brazil – French Guiana – Suriname Border; (8) the Malaria Epidemic in Venezuela; and (9) Updates from the PAHO Public Health Entomology (PHE) TAG.

Main Recommendations

The key outcomes / main recommendations of the Malaria TAG to PAHO are as follows:

- The Malaria TAG reiterated its support for the Plan of Action for Malaria Elimination 2016-2020, and reinforced its commitment towards providing guidance on important technical issues that are relevant to the implementation of the plan.
- The Malaria TAG recommends the M&E Framework for the Region's Plan of Action for Malaria Elimination 2016-2020 be defined in further detail by a working group (convened by PAHO) so that it guides the M&E functions of PAHO as secretariat and coordinator for the implementation of the plan; this undertaking should be completed in accordance with the organization's reporting timeline.
- The implementation of G6PD testing in *P. vivax* confirmed cases should be done in the context of country priorities on a pilot basis in areas of high prevalence of G6PDd, as defined by each country and such that it does not delay provision of safe radical cure in *P. vivax*. Independent of the prevalence of G6PDd, all countries should improve patient education, counseling and pharmacovigilance.
- The Malaria TAG recognizes the importance of the Diagnose-Treat and Detect (DTD) initiative to operationalize implementation of surveillance and response at local level and made specific recommendation for further refinement of the strategy.
- The Malaria TAG concluded that there is currently insufficient high quality evidence to support recommending a presumptive primaquine retreatment strategy in the Americas and emphasized the need to improving adherence to the first course of primaquine treatment as operational approach to prevent relapses. Research studies should be conducted to evaluate whether there is a need for the higher dose primaquine regimen in the Americas.
- The TAG recognized the importance of the findings outlined in the PAHO report that provided updates on the latest results of antimalarial drug resistance surveillance activities; expressed concerns about the potential risk of artemisinin resistance emergence in the Guiana Shield; and encouraged the countries to continue surveillance for antimalarial drug resistance

- The Malaria TAG encouraged PAHO to continue supporting effective malaria elimination efforts in the Guiana Shield; provide specific recommendations regarding the Malakit Project (Cross-Border Pilot Effort on Self-testing and Self-treatment for Malaria among Miners Across the Brazil – French Guiana – Suriname Border); and recommended that PAHO uses WHO mechanisms to address policy and legal impediments, particularly in French Guiana, to access key malaria interventions (especially LLINs) by miners and other vulnerable populations.
- The Malaria TAG recommends, in general, to promote and strengthen cross border surveillance, information sharing, and coordination of interventions in border areas in the Americas
- The Malaria TAG expressed the extreme concern about the gravity of the malaria epidemic in Venezuela and its effects on the whole Region; and stressed the need to ensure adequate supplies of antimalarials, to obtain high coverage with LLINs and purchasing and supplying RDTs for the affected areas. The Malaria TAG did not recommend interventions based on MDA at this time.
- The Malaria TAG joined the Regional Malaria Program in expressing concern about the use of non-recommended interventions for vector control in malaria, particularly fogging, and called for more evidence to support these measures before they are deployed.
- The Malaria Research Agenda should be prioritized and completed as soon as possible; taking note of and integrating the important knowledge gaps that were discussed during the third meeting of the Malaria Technical Advisory Group (TAG).

Specific Outcomes / Recommendations Arising from the Malaria TAG Sessions

Report from the Regional Malaria Program

- The Malaria TAG acknowledged its role in developing the Plan of Action for Malaria Elimination 2016-2020, which was a key focus of the TAG's first and second meetings; and affirmed its commitment towards providing continuing guidance on its implementation.
- Gold mining was noted as an important determinant of malaria in the region and it is suggested that a more systematic way to approach the problem of gold mining and malaria be developed, and that lessons learned on general principles or strategies that show promise be shared as soon as is feasible with member states.
- PAHO is advised to consider the importance of asymptomatic carriers for maintaining transmission as one of the issues that should be subsequently evaluated in each of the countries of the Region. Preliminary studies in eastern Venezuela revealed figures that quadrupled the prevalence of symptomatic patients, which was also experienced and verified in Colombia.
- The importance of the Region's Malaria Research Agenda was likewise emphasized, including the need to integrate the important knowledge gaps that were discussed during the third meeting of the Malaria TAG.
- The TAG further recommends that an online or web-based mechanism be developed for sharing and disseminating the TAG recommendations and other related documents

Regional Guidance on the Implementation of G6PD testing and radical cure in *P. vivax* endemic countries

- With over 6 decades of experience in the use of primaquine in the Americas, there have been very few reports of serious adverse reactions or deaths associated with its empiric use in certain geographic areas. Nonetheless, areas in the region other than these may have a higher prevalence or type of variant (potentially more severe) of G6PD deficiency. Therefore, the Malaria TAG recommends G6PD testing in *P. vivax* confirmed cases on a pilot basis in areas of

high prevalence of G6PDd, especially those with the Mediterranean and other variants associated with severe deficiency, as defined by each country.

- The introduction of G6PD testing should be done in the context of country priorities and basic operational gaps such that it does not delay provision of safe radical cure in *P. vivax*, particularly in Central America
- The implementation of G6PD testing in *P. vivax* confirmed cases in areas with high prevalence of G6PDd as defined by each country should be piloted and promoted with a view towards the potential introduction of tafenoquine, as it becomes available.
- Independent of the prevalence of G6PDd, all countries should improve patient health education, counseling and pharmacovigilance.
- Operational research should likewise be prioritized to facilitate better guidance in this issue, including the following topics:
 - Improved surveillance and reporting for adverse reactions to primaquine based on clinical history and evaluation of hospitalizations and deaths due to *P. vivax* cases
 - Prevalence studies of G6PD deficiency and severity, particularly in specific areas of South America such as Pacific Coast in Colombia and in the Guiana Shield.
 - Additional studies are needed to determine equivalency in efficacy between the 0.5mg/kg for 7 days and 0.25 mg/kg for 14 days primaquine treatment regimens, in that a number of countries are using 0.5 mg/kg for 7 days in the Americas. WHO Guidelines on treatment state that the cumulative dose of primaquine received is the determining factor for *P. vivax* radical cure. A meta-analysis of 7 vs 14 days treatment schemes suggests that they may be equivalent; however, some of these studies were observational (effectiveness rather than efficacy) and further studies are needed, particularly for 7 day treatment.

Updates regarding antimalarial drug resistance surveillance in the Americas

- The Malaria TAG noted the PAHO report that provided updates on the latest results of antimalarial drug resistance surveillance activities. This report indicated the presence of the C580Y mutation in ~2% of samples from Guyana. The TAG recognized the importance of these findings, and encouraged the countries to continue surveillance for antimalarial drug resistance.
- PAHO should provide guidance on the interpretation of results from routine *in vivo* and molecular surveillance.
- Key research activities should include the following topics:
 - Monitoring for the emergence of resistance of *P. vivax* to chloroquine
 - Role of adherence, re-infection, and drug quality as factors related to recurrences

Monitoring and Evaluation Framework for the Plan of Action for Malaria Elimination

- The Malaria TAG acknowledged the importance of the M&E functions of PAHO as secretariat and coordinator for the implementation of the Region's Plan of Action for Malaria Elimination 2016-2020; and advised that the corresponding Monitoring and Evaluation Framework be defined in further detail by a working group (convened by PAHO) in accordance with the organization's reporting timeline.
- Apart from the key indicators approved in the Plan of Action for Malaria Elimination 2016-2020, the M&E framework should also consider the identification of key (malaria elimination) indicators that can be monitored across countries in the Region and are in strong alignment with WHO recommended indicators.

- The M&E framework should also include specific indicators pertaining to border collaboration, migration, social contexts, involvement of private sector, agricultural activities, and other key actions that most pertain to countries that are close to elimination.

Strategy for Early Detection, Treatment, and Case Investigation

- The Malaria TAG recognizes the importance of the Diagnose-Treat and Detect (DTD) initiative to operationalize implementation of surveillance and response at local level, consistent with the recently published WHO Framework for Malaria Elimination as one of the core elements of the malaria programs.
- To make this initiative more relevant and effective, the TAG recommends further refinement of the DTD concept to reflect the following:
 - Reducing time between onset of symptoms and diagnosis/treatment is clearly a key element. In some settings the establishment of a short target timeframe could be unrealistic, especially when cases are few and mostly imported. However, in countries where 48 hours had been already established as operational target, it is important to support such measures.
 - The importance of targeted vector control in response activities should be highlighted.
 - Operational guidance should be developed on how reactive case detection (RCD) will be implemented when triggered by a case or a cluster of cases. Situation specific guidance will need to be developed on diagnostic methods, radius of search, rounds, human resources required, time constraints, role of social actors, the importance of occupational vs household associated risk, and other aspects of the local context.
 - Definition in terms of how the DTD strategy will be monitored and evaluated, including the determination of the cost-effectiveness of RCD.
 - Reconsideration of the initiative's name to better denote the importance of investigation and / or response (e.g. Diagnose-Treat- Investigate) (DTI) rather than Diagnose-Treat and Detect (DTD).
 - The promotion of appropriate balance between “reactive” and “proactive” case detection in accordance with the local epidemiological situation at focus level.
- There is a need to promote operational research to optimize the use of RDTs and proactive case detection, and demonstrate their impact and effectiveness
- The Malaria TAG emphasized the important role of education and strategic communications in this process, and that integration of malaria programs with other health services should continue, particularly in the elimination phase.
- While integration with health service is a key element, the TAG also considered that promotion of such approach in the elimination phase, which places emphasis on the quality and opportunity of the case investigation and prompt response, is a human resource intensive activity that should be supported by actions that enhance specific programmatic capacities in malaria.

Strategy for reducing relapses of *P. vivax*

- Irrespective of adherence, the treatment of all cases of *P. vivax* after a certain period of time following the first treatment regimen is considered “re-treatment”.
- In view of information presented that highlighted the occurrence of relapses at significant rates despite the programmatic use of primaquine at the recommended dosage, and considering information on China's experience with “Spring treatment” (use of presumptive primaquine treatment given to patients who had already completed radical cure and had no evidence of

relapse), the Malaria TAG considered that there is currently insufficient high quality evidence to support recommendation of such retreatment as a strategy in the Americas. The TAG noted that a randomized control trial would need to establish evidence for empiric retreatment before a policy recommendation could be considered. The TAG further noted that:

- Retreatment would likely provide the greatest benefit among those not adhering to treatment in the first cycle, but this group would also likely be at risk for poor adherence when treated the second time.
- A meta-analysis of published studies conducted in the Americas would be useful to document relapse rates when primaquine is given in correct dose.
- Based on evidence available from some studies in Brazil, absorption and poor metabolism of primaquine is also a factor in some relapses, and genetic factors may influence primaquine metabolism.
- Emphasis should be directed to improving adherence to the first course of primaquine treatment.
- Research studies should be conducted to evaluate whether there is a need for the higher dose primaquine regimen in the Americas. Higher dose primaquine (0.5 mg/kg bw /day for 14 days) should be considered for *P. vivax* treatment in the Americas where evidence shows that 0.25 mg / kg bw / day is not effective.
- Surveillance should be strengthened to enable accurate identification of recurrences and relapses.

Cross-Border Pilot Effort on Self-testing and Self-treatment for Malaria among Miners Across the Brazil – French Guiana – Suriname Border

- The Malaria TAG expressed concerns about the potential risk of artemisinin resistance emergence in the Guiana Shield and encouraged effective malaria elimination efforts in the area.
- The Malaria TAG noted the updates shared regarding the Malakit Project (Cross-Border Pilot Effort on Self-testing and Self-treatment for Malaria among Miners Across the Brazil – French Guiana – Suriname Border); recognizes that the proposed project is operationally innovative; and encourages PAHO to continue supporting the three countries in its efforts to contain the transmission of malaria in these border area, including this initiative.
- The Malaria TAG recommended addressing the following aspects / issues:
 - PAHO use PAHO/WHO mechanisms to approach France with a request that it resolve policy / legal impediments to access key malaria interventions (especially LLINs) of miners and other vulnerable populations in French Guiana ,
 - TAG was concerned that misuse of antimalarials in the Malakit Project could lead to emergence of ACT resistance and should be carefully monitored / evaluated as an integral part of the project activities
 - The project needs to strengthen the M&E design for the pilot in order to have conclusive results.
 - Review and reinforce aspects related to coverage of the at risk population, frequency of visiting resting places where the at risk population will be reached, inclusion of prevention tools as part of the kit / intervention (LLINs), understanding of places where transmission is occurring, effects on *P. vivax* transmission, and use of ACT alternatives that may promote better adherence than that achieved with ART+LUM.

Malaria Epidemic in Venezuela

- The Malaria TAG expresses extreme concern about the gravity of the situation in Venezuela and its effects on the whole Region.
- It is paramount to determine what Venezuela considers as a priority actions required to address the current malaria situation in the country. Whatever interventions are undertaken, there must be the political commitment to sustain them.
- The Malaria TAG did not recommend interventions based on MDA at this time. As assessed from the situation report submitted by PAHO, the operational conditions to conduct a MDA do not exist in the municipalities proposed for this intervention given lack of personnel and serious concerns regarding the sustainability of post-MDA follow-up.
- If at some point MDA becomes a feasible alternative because the operational conditions are guaranteed and the basic intervention is properly implemented, additional issues to be addressed include a clear definition of the target population, defined outcomes and the timeframe for their achievement, along with a plan for what interventions need to be in place following a time-limited MDA program, including the political commitment to sustain those interventions.
- The priority approach at this time should be to ensure adequate supplies of antimalarials, obtain high coverage with LLINs and purchasing and supplying RDTs in the epidemic areas.

Updates from the Public Health Entomology TAG

- The TAG joined the Regional Malaria Program in expressing concern about the use of non-recommended interventions for vector control in malaria, particularly fogging in settings with low coverage of LLIN and IRS. The TAG called for more evidence to support these measures.
- Understanding the importance of IRS as a core intervention in malaria and the low coverage in some endemic areas in the Region, it is necessary to review and update the entomological evidence, particularly related to resting behavior from some settings in Central America that could be arguing against the utility of IRS
- Vector control interventions in malaria, including LLIN and IRS, must be adapted to the local context.