

WHO Technical Consultation on research requirements to support policy recommendations on highly sensitive malaria diagnostic tests

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Update on the Technical Consultation to be held in May 2018, Geneva, Switzerland

Background

In May 2017, WHO convened an Evidence Review Group (ERG) on low-density malaria infections with the aim of revising current recommendations on the use of malaria diagnostics in low transmission settings, based on the most recent data on the natural history, prevalence and contribution to transmission of low-density *P. falciparum* and *P. vivax* infections.

The conclusions, endorsed by the Malaria Policy Advisory Committee (MPAC) in October 2017, recommended quality-assured conventional RDTs and microscopy for the confirmation and management of malaria cases and malaria surveillance, including routine health information systems and household surveys, in all epidemiological situations. The ERG also recommended that highly sensitive techniques capable of detecting low-density infections (below 100 parasites/μl) be used only for research purposes until there is sufficient evidence that using these tools to detect low-density infections will have a significant impact on transmission.

The ERG recommended additional research to address knowledge gaps on the relative importance and contribution to transmission of low-density infections and to define the public health impact of strategies incorporating highly sensitive diagnostic tests in different epidemiological settings. While the ERG fell short of defining study design characteristics, it identified a series of specific epidemiological research questions that need to be addressed, as listed in the Annex below.

The participants agreed that many of these epidemiological research questions are unlikely to be answered in the very near future and so identified the following research questions with programmatic application:

- a. What impact on transmission is achievable by actively detecting and eliminating all infections, including low-density malaria infections, using highly sensitive point-of-care diagnostics in low transmission settings, particularly in areas of low vectorial capacity, compared to conventional malaria elimination methods (i.e., universal access to diagnosis and treatment and vector control, MDA, and active or reactive screen-and-treat campaigns using less sensitive point-of-care diagnostics)?

- b. In low and very low transmission settings, what is the proportion (or number) of infections that need to be detected and treated in order to accelerate the reduction of transmission towards malaria elimination?
- c. What is the cost–benefit for health systems in using highly sensitive diagnostics for specific target groups and in elimination settings? What are the most cost–effective deployment strategies for highly sensitive diagnostics in different settings?

Building on this work, in order to clarify the public health impact of detecting low-density malaria infections using highly sensitive diagnostic tests, WHO plans to convene a Technical Consultation on the research requirements to support its policy recommendations on highly sensitive malaria diagnostic tests.

Objectives of the Technical Consultation

1. To define the research needed to conclude that strategies incorporating highly sensitive diagnostic tests will:
 - a. have a significant impact on malaria transmission in areas working towards elimination when used in passive case detection, reactive case detection, proactive case detection, mass screening and treatment;
 - b. prevent re-establishment of malaria transmission; and
 - c. prevent adverse effects of malaria in pregnancy.
2. To propose feasible study designs to prove that strategies incorporating highly sensitive malaria diagnostics can: i) have an impact on malaria transmission and contribute to elimination; ii) prevent the re-establishment of transmission; and iii) prevent adverse effects of malaria in pregnancy.
3. To review the current landscape of research on the use of highly sensitive malaria diagnostic tests, including study design of recently completed, ongoing and planned studies.
4. To develop a realistic timeline, based on the findings of ongoing, planned and newly identified study requirements, for generating the evidence on the impact of using highly sensitive malaria diagnostics in a range of transmission settings and use scenarios.

Process

Three GMP units, Prevention Diagnostics and Treatment together with Elimination and Surveillance, will collaborate on the technical preparations for the meeting. The PDT unit will also provide administrative support, with support from the Bill & Melinda Gates Foundation umbrella grant.

WHO/GMP will convene a group of 12 independent experts in diagnostics, surveillance and elimination from national malaria programmes and leading technical agencies, as well as experts in malaria applied field research methodology from academic institutions in order to address Objectives 1 and 2 of the meeting.

Representatives of PATH, FIND and multiple research institutions (e.g. LSHTM, Radboud University Medical Center of The Netherlands, LSTM, UCSF, CDC Atlanta and MESA Alliance) will be invited to present ongoing and planned studies on highly sensitive malaria

diagnostic tests in order to address Objective 3 of the meeting. A select number of representatives from these institutions will be invited to prepare thematic overviews of ongoing and planned studies.

The consultation will involve up to 25 participants and will require 3 days. Following the advice and recommendations of the MPAC in April 2018, the tentative dates proposed for the meeting are 28–30 May 2018.

At the meeting, the WHO Secretariat will share with participants the current recommendations on the use of malaria diagnostics for case management, chemoprevention, elimination and surveillance based on current evidence reviews and guidelines. This will provide the current policy context and guide participants in the definition of feasible studies through which to demonstrate the eventual impact of highly sensitive diagnostic tests in tracking and treating low-density infections.

Annex

Epidemiological research questions identified by the ERG on low-density malaria infections convened by WHO in May 2017

1. What is the proportion and absolute number of low-density infections in low and very low transmission settings (0–5% prevalence by PCR), and what is the spatial distribution of malaria infections?
2. What is the relationship between the proportion of low-density infections and recent history of transmission, i.e., is an inflection point reached in the proportion of low-density infections detected by highly sensitive diagnostics in areas with sustained reduction of transmission at very low levels?
3. What is the proportion of low-density asymptomatic infections that become symptomatic as part of the natural history of infection in different endemic settings?
4. What is the prospective clinical and pathological impact of untreated low-density parasitaemia?
5. What are the risk factors for persistence, and what is the role of low-density infections in the spread of antimalarial resistance?
6. Can novel molecular techniques such as amplicon sequencing aid in investigating the natural history of infections, e.g., by measuring clonal parasite density, and in investigating relapse–reinfection epidemiology?
7. In the natural history of infections, what is the duration of infectiousness (particularly in low-endemic settings) and what are its major determinants?
8. What are the main determinants – related to host, vector and parasite – of infection success in experimental mosquito-feeding experiments and of making those mosquitoes infectious for humans? What is the relationship between parasite density and infectiousness for different vector species? What are feasible study designs with which to achieve meaningful numbers in low-endemic settings?