

Proposed WHO Technical Consultation on research requirements to support recommendations on highly sensitive malaria point of care diagnostic tests



Malaria Policy Advisory Committee (MPAC) Meeting

11 – 13 April 2018

Salle A, World Health Organization, Geneva, Switzerland

Global **Malaria** Programme



**World Health
Organization**



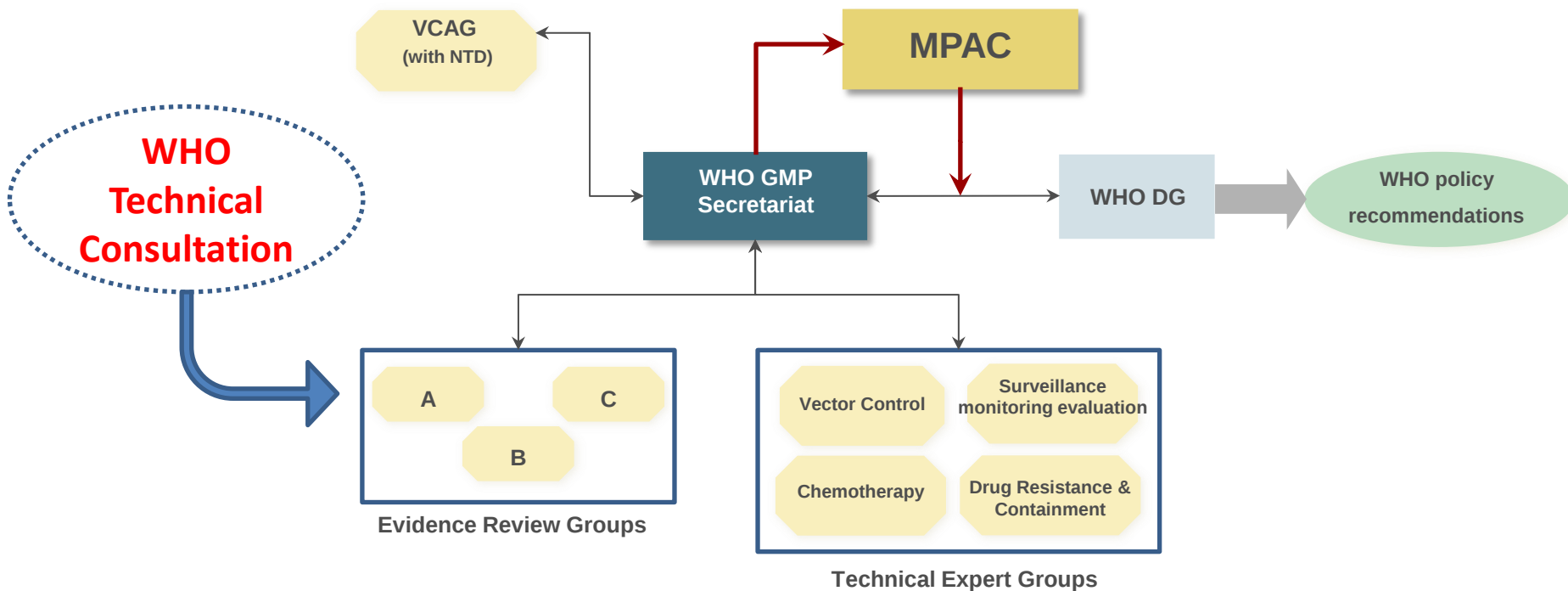
Outline of the presentation

- Recap of relevant WHO recommendations
- Unanswered epidemiological and programmatic questions
- Objectives of the Technical Consultation
- Evidence-base to generate WHO guidance on in-vitro diagnostics
- Process for the WHO Technical Consultation



- 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/ μ l) 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.

WHO policy making process for malaria





- The ERG recommended additional **research to understand the 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.** The ERG identified a series of basic epidemiological research questions that need to be addressed, namely:
 - 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 their spatial distribution?
 - What is the relationship between the proportion of low-density infections and recent history of transmission?
 - What is the proportion of low-density asymptomatic infections that become symptomatic as part of the natural history of infection in different endemic settings?
 - What is the prospective clinical and pathological impact of untreated low-density parasitaemia?
 - What are the risk factors for persistence, duration of infectiousness and what is the role of low-density infections in the spread of antimalarial resistance?
 - Can novel molecular techniques such as amplicon sequencing aid in investigating the natural history of infections?
 - What are the main determinants – related to host, vector and parasite – of infection success in experimental mosquito-feeding experiments and forward transmission to humans?



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

1. 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, when deployed in addition to conventional malaria elimination methods (i.e., universal access to diagnosis and treatment and vector control, MDA, and active or reactive case detection using less sensitive point-of-care diagnostics)?
2. 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 rapidly reduce malaria transmission, contributing to malaria elimination?
3. 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?



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 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.



In the context of developing a WHO List of Essential in-vitro diagnostics (IVD), WHO commissioned a review of key guidelines for diagnostics for Malaria, Tuberculosis, HIV, Hepatitis B and C and Syphilis.

MAIN FINDINGS *

1. *It was clear that the **majority of evidence considered in IVD guidelines has been of diagnostic test accuracy, and not the impact of testing.** Thus test accuracy is the main focus of our review.*
2. *However, we have noted where evidence of the impact of tests, whether either from trials, observational studies or predicted from decision analysis models is included as it may provide stronger evidence of the benefits and harms of testing.*
3. *Similarly, we identified the inclusion of studies other than field test accuracy studies such as WHO internal validation studies of test performance.*

* Deeks J., Mallett S., Takwoingi S. (2018). *Refining and harmonizing processes for assessment and reporting of evidence for IVD use in WHO guidance documents*. Test Evaluation Research Group, Institute of Applied Health Research, University of Birmingham.

Potential uses of HS POCT for malaria



	Malaria transmission intensity			
Potential Use	Zero & receptive	Very low transmission	Low transmission	Moderate to high transmission
Diagnosis				
Risk maps				
Border				
MSAT/FSAT				
ACD in risk groups				
RACD				
HH surveys				
MiP				
ISTp/SSTp				

Process for the WHO Technical Consultation



- Three GMP units, Prevention Diagnostics and Treatment together with Elimination and Surveillance, will collaborate on the technical preparations for the meeting.
- WHO Secretariat will present use scenarios of malaria diagnostics for case management, chemoprevention, elimination and surveillance based on current guidelines.
- The consultation will include 12 independent experts in diagnostics, surveillance, elimination and malaria in pregnancy 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.
- A select number of representatives from of PATH, FIND and multiple research institutions (e.g., LSTM&H, Radboud University Medical Center of The Netherlands, LSTM, UCSF and MESA Alliance) will be invited to present overviews of ongoing and planned studies on highly sensitive malaria diagnostic tests to address the Objective 3 of the meeting.
- In working groups dedicated to the three specific objectives, participants will discuss **feasible study designs** to demonstrate the eventual impact or test accuracy of highly sensitive diagnostic tests when used in different transmission settings.
- In total, the ERG meeting will involve up to 25 participants and will require 3 full working days. Following the advice of the MPAC, the tentative dates proposed for the meeting are 30 May – 1 June 2018.



Discussion