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

4 - 6 June 2018

Room D46025, WHO/UNAIDS Building D, Geneva, Switzerland

Global **Malaria** Programme

World Health Organization

Relevant WHO recommendations - 2017

- In May 2017, WHO convened an Evidence Review Group (ERG) on low-density malaria infections to review 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. MPAC 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.

Unanswered epidemiological questions

- The 2017 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 at are the main determinants – related to host, vector and parasite – of infection success in experimental mosquito-feeding experiments and forward transmission to humans?

Unanswered programmatic questions

The 2017 ERG 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)?

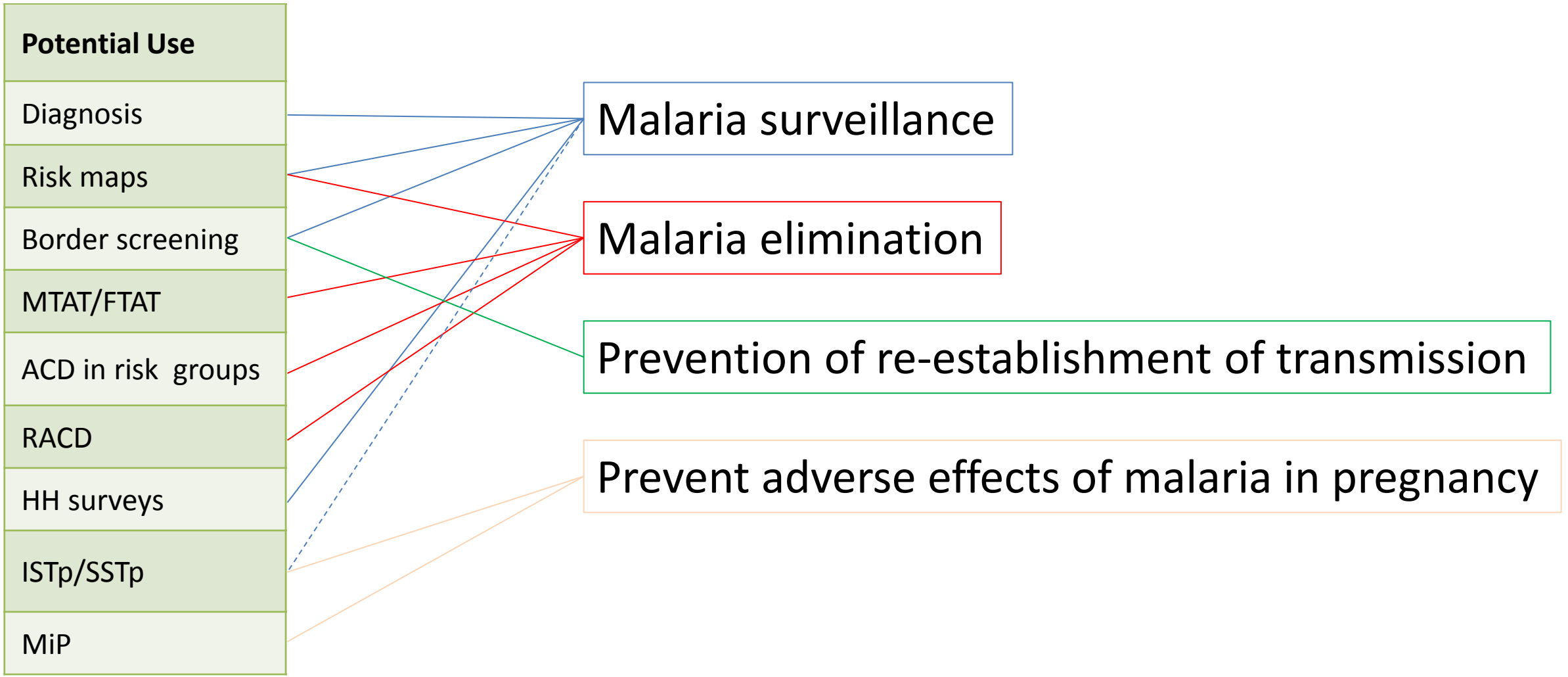
2. In low and very low transmission settings, what is the proportion (or number) of infections that need to be detected and treated in order to rapidly reduce malaria transmission, contributing to malaria elimination?

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?

Objectives of the Technical Consultation in 2018

1. To define the key research questions needed to conclude that strategies incorporating highly sensitive point-of-care diagnostics for falciparum malaria 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 testing and treatment;
   b) prevent re-establishment of malaria transmission; and
   c) prevent adverse effects of malaria in pregnancy.
2. For each of the identified research questions, define most appropriate transmission setting, accounting for seasonal variation and recent history of transmission, study methodology to acquire direct or indirect supportive evidence, including study outcomes, comparators, co-variates and sample size requirements.
3. To review the current landscape of research on the use of highly sensitive malaria diagnostic tests, including recently completed and ongoing 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.

Potential uses of HS POCT for falciparum malaria



Potential uses of HS POCT for falciparum malaria

	Malaria transmission intensity				
Potential Use	High (≥ 35% *Pf*PR)	Moderate (10-35% *Pf*PR)	Low (1-10% *Pf*PR)	Very low (>0 but < 1% *Pf*PR)	Zero and receptive
Diagnosis	II	II	II		
Risk maps			IIII		
Border screening					
MTAT/FTAT			IIII		
ACD in risk groups			II		
RACD			II		
HH surveys					
ISTp/SSTp					
MiP		III	III		

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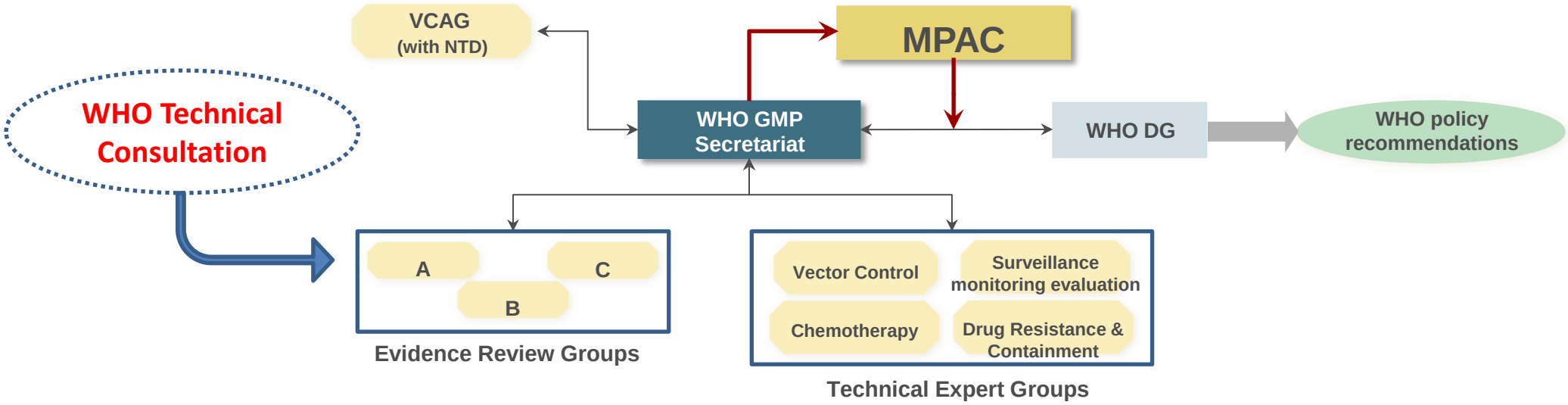
Study outline in Annex 3 of the Report of the Technical Consultaiton

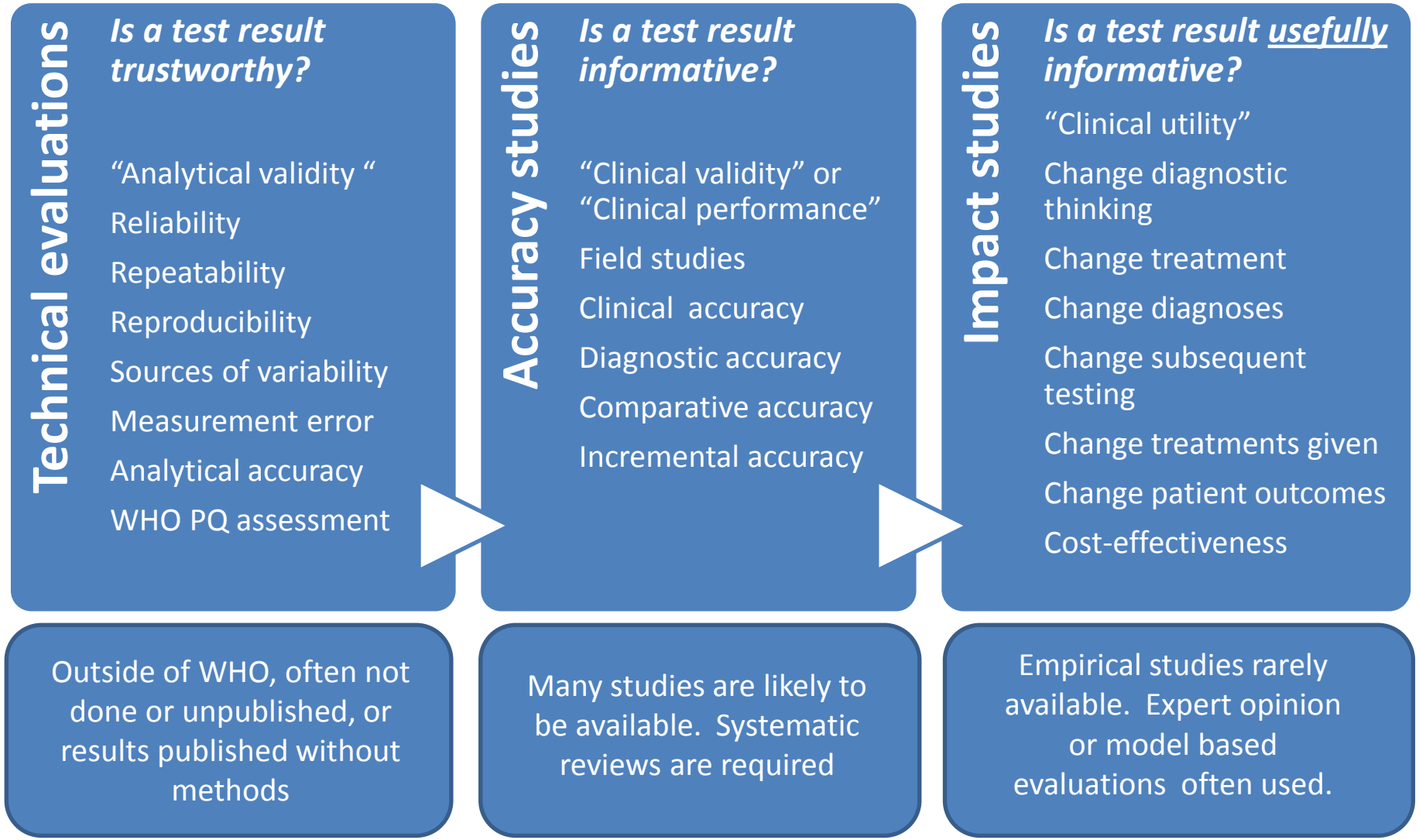
World Health Organization

Process for the WHO Technical Consultation

- The Prevention Diagnostics and Treatment, Elimination and Surveillance Units collaborated in the preparations of the meeting.
- The consultation includes 9 independent experts in diagnostics, surveillance, elimination and malaria in pregnancy as well as experts in malaria applied field research methodology and modelling, 10 participants from PDPs and research institutions involved in R&D on highly sensitive malaria diagnostic tests, 7 Observers form funding agencies, NGOs and academic institutions and 7 members of WHO secretariat.
- Three days meeting with Day 3 as closed session for independent experts and WHO secretariat

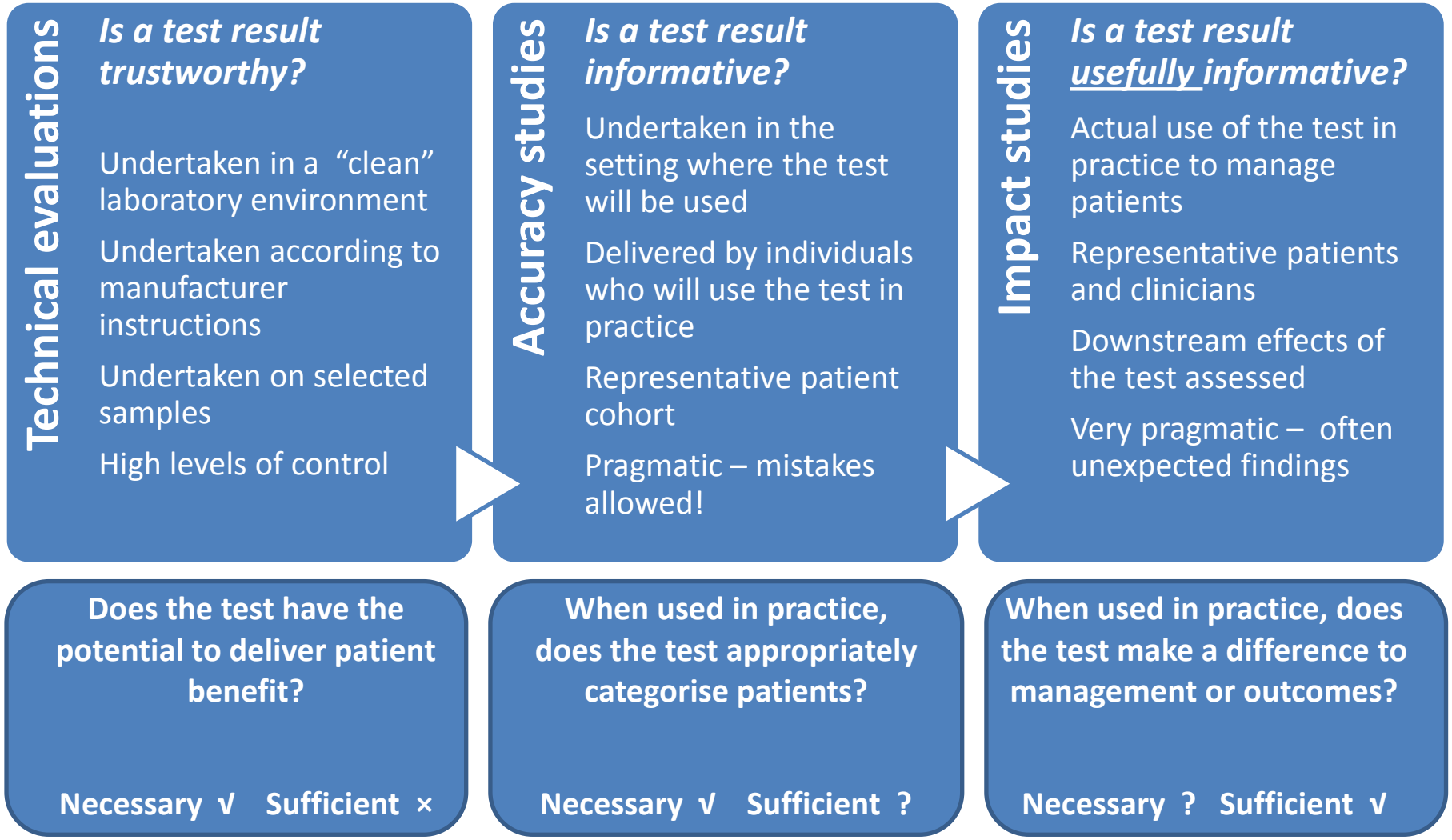


Assessing evidence on in vitro diagnostics (IVD)



Courtesy of Jon Deeks, Professor of Biostatistics, Institute of Applied Research, University of Birmingham

Assessing evidence on in vitro diagnostics (IVD)



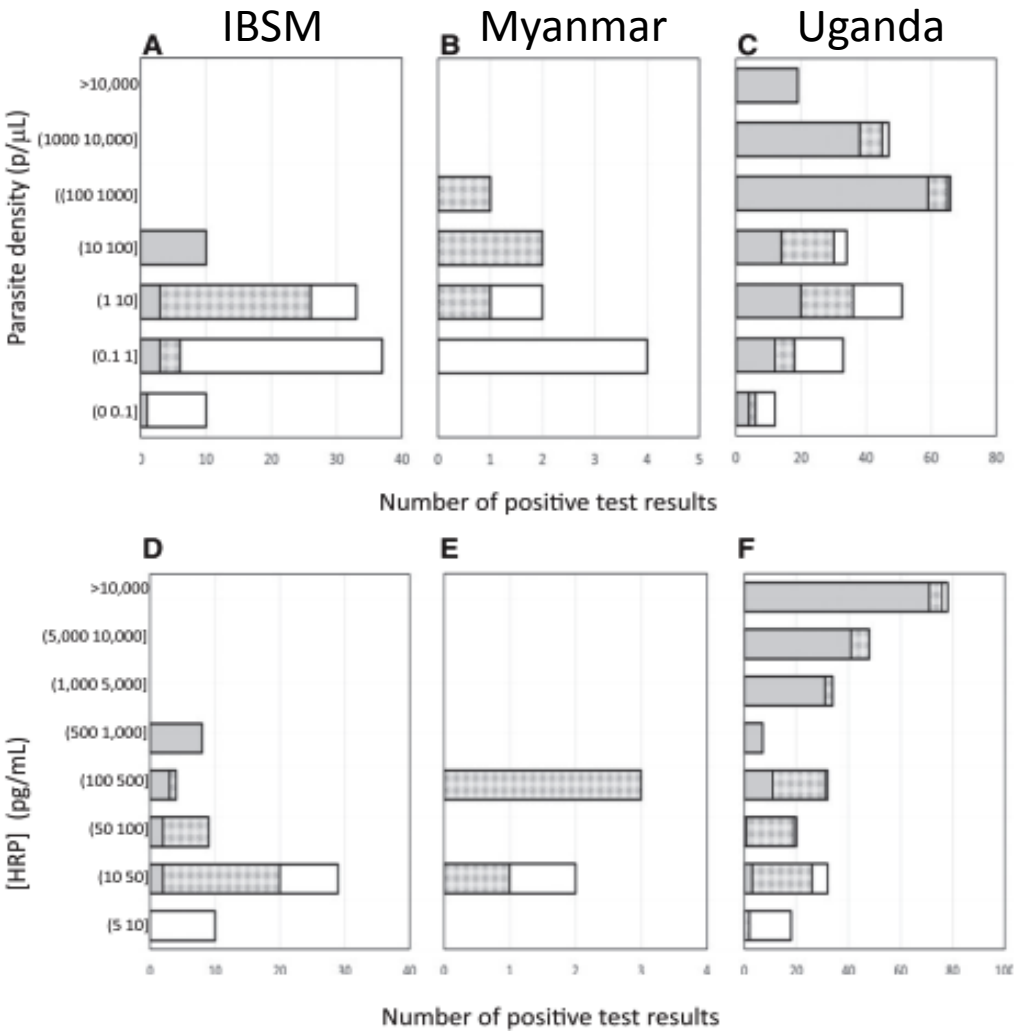
Courtesy of Jon Deeks, Professor of Biostatistics, Institute of Applied Research, University of Birmingham

Considerations by the Technical Consultation

- For the assessment of evidence on IVDs, analytical validity should first be assessed in controlled laboratory conditions, followed by field-based accuracy studies to determine diagnostic and clinical performance in the settings and populations of intended use.
- The most challenging are impact studies, assess the role of diagnostics as a part of specific health interventions and the effects on patient or community outcomes. The impact depends critically on a number of intermediate factors, including, but not limited to, the effect on diagnostic and treatment decisions by the healthcare provider as well as effectiveness of treatment delivery. In low transmission settings, impact studies may require prohibitively large sample sizes.
- Impact studies may still be needed if the adequate evaluation of diagnostic accuracy is not feasible in the absence of a well-established reference standard, or when the link between the test result and the treatment/intervention are unclear or if the impact of the test on public health outcomes can occur through multiple routes.

Few published diagnostic accuracy studies

- Studies based on samples from Uganda and Myanmar showed increased sensitivity of the Alere™ Malaria Ag *Pf* test compared with the Standard Diagnostics Bioline Malaria Ag *Pf* test. However, clinical sensitivity of the Alere™ Malaria Ag *Pf* test was highly dependent on the distribution of parasite and HRP2 densities in the sampled population, which varied by transmission setting.

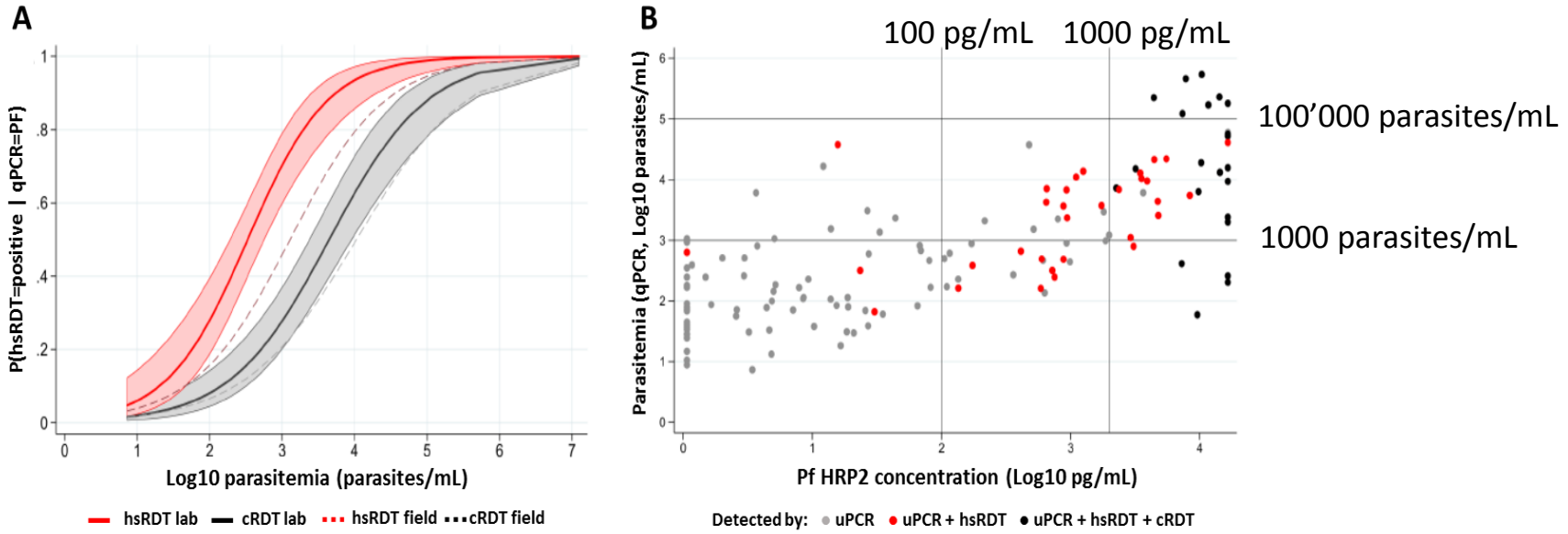


Distribution of Alere™ Malaria Ag *Pf* test samples by parasite density and HRP2 concentration from blood-stage malaria challenge studies (A, D), Myanmar study (B, E) and Uganda study (C, F).

positive by qRT-PCR, hsRDT and cRDT positive by qRT-PCR and hsRDT Positive by qRT-PCR only

Das *et al. Am J Trop Med Hyg.* 2017; *97*:1540–50

Few published diagnostic accuracy studies



A. Probability of a *P. falciparum* positive test result by Alere™ Malaria Ag *Pf* test (hsRDT, red) compared to the Standard Diagnostics Bioline Malaria Ag *Pf Pv* test (cRDT, black) in the laboratory (continuous lines) and field (dotted lines) according to the parasitaemia of *P. falciparum* mono-infections, measured by ultra-sensitive PCR (uPCR).

B. Increased range of *Pf*HRP2 concentration (measured by Quansys ELISA) detected by Alere™ Malaria Ag *Pf* test compared to the Standard Diagnostics Bioline Malaria Ag *Pf Pv* test performed in the field. Vertical lines indicate *Pf*HRP2 concentrations of 100 pg/mL and 2000 pg/mL, while horizontal lines correspond to 1000 parasites/mL and 100 000 parasites/mL.

Landier *et al. J Clin Microbiol.* 2018; *56:* e00565-18

Conclusions proposed by the Technical Consultation

1. To evaluate the role of HSPOCTs in surveillance and elimination strategies, and the prevention or treatment of MiP will require impact studies assessing the public health and clinical benefit of such interventions. This includes evaluating the effects on patient and/or community outcomes, diagnosis and treatment, as well as cost-effectiveness. While impact studies are the most informative for policy decisions, they are also the most complex in design and may not be feasible in many settings. To help address these constraints, modelling-based studies may provide insights into potential impact in areas of low and very low transmission.

2. Any new malaria diagnostic tests, including both HSPOCTs and cRDTs, should ideally meet the ASSURED criteria: Affordable by those at risk of infection, Sensitive (few false-negatives), Specific (few false-positives), User-friendly (simple to perform with minimal training), Rapid (to enable treatment at point of care) and Robust (no need for refrigerated storage), Equipment-free, Delivered to those who need it

3. Impact studies should follow independent HSPOCT performance assessments through: i) laboratory studies using well-characterized reference samples of known parasite and antigen concentrations, and ii) a systematic review of field-based accuracy studies across a range of transmission settings.

Priority studies to evaluate the **accuracy** of HSPOCTs

4. To define sensitivity and specificity for detecting malaria in different settings and use case scenarios, studies comparing HSPOCTs to cRDTs using quality-assured methods as reference standards (e.g. quantitative PCR, ELISAs, multiplex bead-based immunoassays) should be implemented in a range of:

   i. transmission intensities and degrees of seasonality;

   ii. target populations (e.g. high-risk occupations, mobile or migrant populations); and

   iii. health care system levels (e.g. public and private facilities, community services).

   These studies ideally should follow standardized protocols and employ reference assays to enable comparability across studies or diagnostic tests and assessment of the impact of HRP2 persistence on test accuracy, where feasible and relevant.

To assess **impact** of HSPOCTs in elimination strategies

5. To assess the potential applications of HSPOCTs in accelerating elimination (i.e. “rapid” reduction in transmission of indigenous cases), cluster randomized trials (CRTs) were proposed comparing HSPOCTs to cRDTs when used in mass test-and-treat (MTAT) strategies. These studies should estimate:

   i. the number and proportion of additional cases detected and treated, and

   ii. the impact on reducing malaria transmission based on trends in passively detected clinical cases (confirmed by cRDTs or microscopy) at health facilities in the same area.

   Relevant CRTs include stepped-wedge, cross-over and factorial designs. Due to the large sample sizes required for measuring reductions or interruptions in transmission in low to very low transmission settings, indirect evidence can be gathered from trials conducted in moderately endemic settings where changes in transmission (e.g. incidence, prevalence or other relevant measures) can be more easily quantified. Modelling-based studies may also be able to provide insights into potential impact.

To assess **impact** of HSPOCTs in surveillance and MIP

6. To assess the potential role in surveillance for elimination, studies were proposed evaluating the effectiveness of HSPOCTs vs. cRDTs in identifying additional foci of transmission through reactive case detection (RACD) or proactive case detection (PACD) for a targeted response beyond what is possible using cRDTs and microscopy.

7. To provide preliminary evidence on the impact of first-trimester low-density malaria infections detectable with HSPOCTs on pregnancy outcomes, a retrospective study of samples from a cohort of women, followed from pre-conception through to delivery, is ongoing. High-quality evidence on the potential role of HSPOCTs in testing for MiP will require individually randomized controlled trials (RCTs) on the effectiveness of HSPOCTs vs. cRDTs when used for early detection and treatment in the first trimester of pregnancy in moderate to high transmission settings.

Other considerations

- In areas of low transmission, there are limited data on the natural history of infection and longitudinal infection dynamics. However, studies are currently being implemented and planned in multiple African settings. These seek to understand the epidemiology of low-density infections in relation to clinical illness, detectability throughout the course of infection, acquisition of protective immunity, and duration of infectiousness. The outcomes of this research should be followed closely to inform how the use of HSPOCTs in the detection and elimination of all infections (including those with low parasite density) may affect malaria transmission.
- Several other applications for HSPOCTs were considered but determined to be of lower priority. These include the use of HSPOCTs in border or port-of-entry screening to prevent importation of malaria parasites, in clinical case management, and in intermittent test-and-treat strategies for MiP (including in HIV coinfections).

Discussion