# Good Practices for Selecting and Procuring Rapid Diagnostic Tests for Malaria

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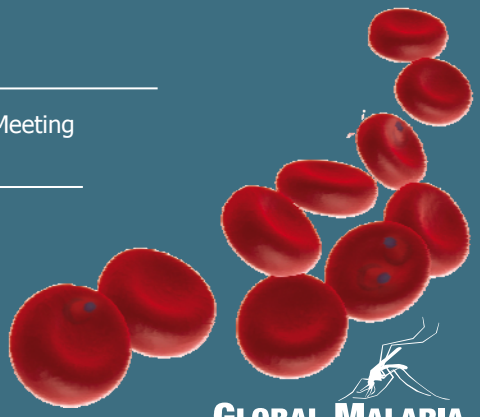
Silvia Schwarte
Diagnosis, Treatment and Vaccines
Global Malaria Programme



World Health Organization

GLOBAL MALARIA PROGRAMME

## Good Practices for Selecting and Procuring RDTs for Malaria

- The **target audience** for this manual includes procurement officers, malaria programme managers, health officers and supply chain managers responsible for selecting, procuring or assisting in the procurement of RDTs for malaria in the public and private sectors.
- The manual summarizes information from publications on the quality of malaria RDTs that is readily accessible only by specialized procurement agencies. Its **aim** is to improve understanding of the following aspects of procurement:
  - performance components and selection criteria;
  - estimating quantity requirements and budgeting;
  - defining technical specifications;
  - managing tenders, adjudications and contracts;
  - quality control through lot testing;
  - supply management and product recalls; and
  - monitoring supplier performance and managing product variations.

# Vulnerabilities…

## … of specific RDT components

**Table 1. Vulnerability of various components of rapid diagnostic tests for malaria**

| Component | Characteristics that can make a product vulnerable |
|---|---|
| Nitrocellulose membrane[a] | Variation in pore size (can affect flow of antibody–antigen complex and clearance of blood) |
| Signal antibody | Stability of conjugation to label (e.g. colloidal gold) |
| | Amount of antibody on strip (affects test line intensity) |
| | Purity |
| | Innate ability of selected antibody to bind specific target of interest and not others |
| | Antibody stability |
| | Consistency and variability in manufacture |
| Capture antibody | Ability to adhere to membrane |
| | Amount of antibody on strip (affects test line intensity) |
| | Purity |
| | Affinity of the selected antibody for the target antigen |
| | Specificity of the antibody for the target antigen |
| | Antibody stability |
| | Consistency and variability in manufacture |
| Buffer, lysing agent and additives | Composition (can affect the stability of antibodies, neutralize agents that cause false-positive reactions and control red cell lysis to release antigens) |
| | Viscosity (can affect assay reaction rate) |
| | Variation in composition can affect RDT performance (influence antigen–antibody binding)[b] |
| | Required volumes, packaging and unit dose of buffers can vary among RDTs |
| | The shelf life of the buffer may be different from that of the RDT |
| Cassette housing | Placing of sample well controls blood contact with the signal antibody and varies by device |
| | Compression of nitrocellulose membrane (can inhibit flow) |
| | Presence, absence and placement of evaporation holes (can affect flow and reduce late back flow) varies by device |
| Packaging | Packaging (must exclude humidity to avoid degradation of RDT) |
| Buffer volume | Number of drops of buffer solution (controls flow and sometimes lysis bu does not control the speed of development of the results) |
| Blood volume | Amount of blood transferred to the RDT (can affect the availability of the target antigens if low volume, and can reduce the clearance of blood reducing clarity of results, if excess volume) |

## … in procurement of RDTs

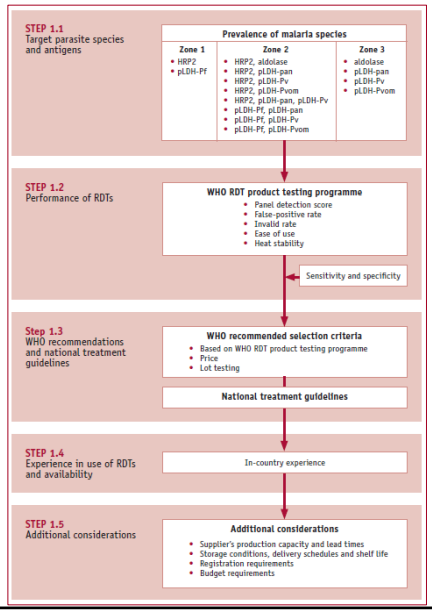
**Table 2. Vulnerability in procurement of rapid diagnostic tests for malaria**

| Step | Procurement vulnerability |
|---|---|
| Selecting an appropriate RDT | Selecting HPR2-detecting RDTs for areas of prevalent falciparum and non-falciparum malaria |
| | Selecting combination RDTs for areas with predominantly falciparum malaria |
| Quantification | Overestimating requirements |
| | Underestimating requirements |
| Budgeting | Underestimating costs of transport, storage and distribution |
| | Poor compliance with procedural requirements of funding agencies |
| Technical specifications | Lack of specifications on diagnostic performance requirements |
| | Missing information on RDT format |
| | Missing thermal stability requirements |
| | Missing requirements for completeness of kit |
| Procurement method | Open tender, leading to multiple offers not relevant to conditions of use and extended bid evaluation timelines |
| | Direct procurement from limited suppliers, leading to limited choices and risks for high prices and delays |
| Inviting tenders | Limited use of the assessment made by the WHO product testing programme |
| Contracts | Missing specifications on manufacturer's liability for replacement of delivery of defective products |
| | No reference to lot testing and its performance requirements |
| | No specification of temperature requirements for transport and storage |
| | No staggering of deliveries |
| | Wrong timing of deliveries in relation to malaria transmission season or training of health workers |
| Evaluating bid response | Assessment of diagnostic performance based on insufficient documentation submitted by the manufacturer |
| | No involvement of malaria RDT experts in assessing compliance of the product to technical specifications set in the tender |
| | No submission or evaluation of RDT samples submitted by manufacturers |
| | Poor evaluation of production capacity and financial viability of the supplier |
| Lot testing | Post-shipment lot testing performed after arrival in the country of use without specification of liability for replacement in contractual agreements with manufacturer |
| Transport and port clearance | No specifications to forwarding agent for temperature requirements during transport by air or sea (e.g. in refrigerated containers) |
| | No specifications to clearing agent for temperature requirements during port clearance and customs procedures |
| | Delays and demurrage costs due to insufficient preparation of port clearance procedures |

# Procurement Checklist

| Steps | Procurement activity | Responsible entity |
|---|---|---|
| 1 | Requirements for selecting RDTs | NMCP |
| 2 | Estimating needs | NMCP + forecasting team |
| 3 | Budgeting and budget components | NMCP |
| 4 | Defining technical specifications | NMCP |
| 5 | Procurement method and tender documents | Procurement Unit + NMCP |
| 6 | Inviting tenders | Procurement Unit |
| 7 | Evaluating bids and awarding contracts | Procurement Unit + NMCP |
| 8 | Quality assurance in procurement | Procurement Unit |
| 9 | Quality control by lot testing | Procurement Unit |
| 10 | Transport, port clearance and receipt | Procurement Unit + Supply |
| 11 | Monitoring | Procurement Unit + NMCP |
| 12 | Continuous improvement | Procurement Unit + NMCP |

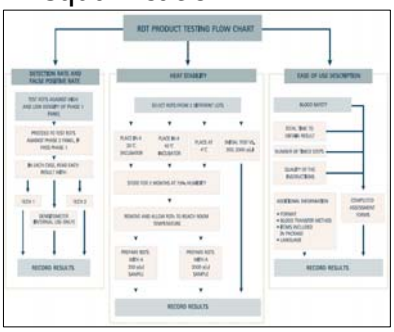
# Step 1
## Selection of an appropriate RDT




# 1.2 WHO/FIND Malaria RDT Performance Testing Programme

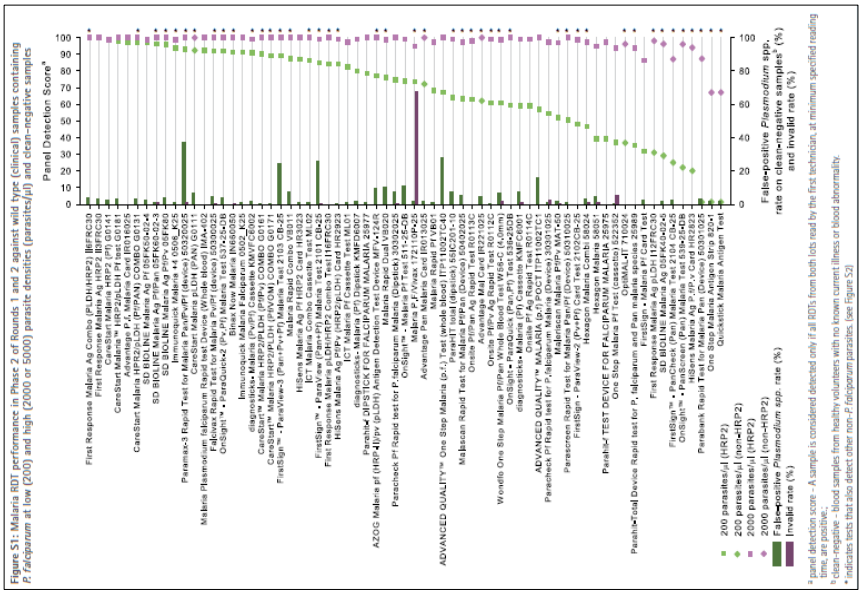
Programme operational since 2008. Offers an established mechanism that allows laboratory-based evaluation of RDT performance in a standardized way => Distinguish between well and poorly performing tests in order to guide procurement and prioritization for entry into WHO Prequalification

**Evaluation criteria:**
- Panel Detection Score (PDS) at 2000 and 200 parasites/µL
- False Positive Rate
- Invalid Rate
- Heat stability
- Ease of use



# RDT performance in Phase 2 of Rounds 1 and 2

against wild type (clinical) samples containing *P. falciparum* at low (200 parasites/µl) and high (2000 or 5000 parasites/µl) parasite densities and clean-negative samples




a panel detection score - A sample is considered detected only if all RDTs from both lots read by the first technician, at minimum specified reading time, provide positive results.

b clean-negative - blood samples from healthy volunteers with no known current illness or blood abnormality.

* indicates tests that also detect other non-*P. falciparum* parasites. (see Figure S2)

# 1.3 WHO recommended selection criteria for procurement of RDTs


1. *Plasmodium* species and transmission intensity
   - 1.1 For detecting *P. falciparum*
     - 1.1.1 In areas of low and moderate transmission: It is highly advisable to select RDTs with a *P. falciparum* panel detection score well above 50% at 200 parasites per microlitre (e.g. > 75%).
     - 1.1.2 In areas of high transmission: The *P. falciparum* panel detection score should be at least 50% at 200 parasites per microlitre. As the extent of high-transmission areas is likely to decrease with effective malaria control, a panel detection score well above this level should become the basis for product selection in the future.
   - 1.2 For detecting *P. vivax*: The panel detection score for *P. vivax* should be equivalent to that for *P. falciparum*: well above 50% at 200 parasites per microlitre (e.g. > 75%).
2. False positive rate less than 10%
3. Invalid rate less than 5%


## Further considerations:

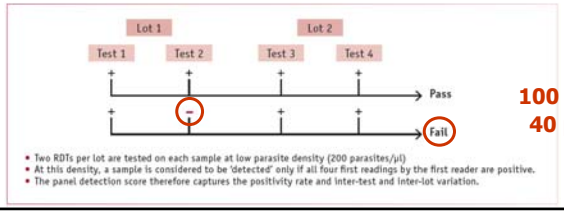
- Stability
- Ease of use and training requirements
- Price
- Lot testing (Step 9)

# Limitations of using sensitivity from RDT field trials (I)

## Definitions

- **Sensitivity:** Percent of patients with the infection who will have a positive result in the test under evaluation, determined from the result of the reference or 'gold standard' test.
- **Panel detection score:** A score between 0 and 100, calculated as the proportion of times a malaria RDT gives a positive result on all tests from both lots tested against samples of parasite panels at a specific parasite density (i.e. four tests at 200 parasites/µL, two at 2000 parasites/µL). Invalid tests are excluded from the analysis.

FIGURE 1
**Determination of panel detection score at low parasite density (200 parasites per microlitre)**




**Reading against:**
**100 panels of Pf at 200 parasites/µL**
**40 panels of Pv at 200 parasites/µL**

# Limitations of using sensitivity from RDT field trials (II)

Published results of RDT field trials might vary in sensitivity and specificity because of:

- parasite density in the study population (RDT sensitivity depends on the antigen concentration and decreases at low parasitaemia),
- heterogeneous diagnostic performance of the comparison method (usually microscopy),
- inconsistent manufacturing standards for the RDT used in the study,
- exposure of the RDT to high temperatures during distribution and storage before the study, and
- problems with RDT preparation or interpretation of results.

**PANEL DETECTION SCORE IN RELATION TO SENSITIVITY**

The *panel detection score* is a standardized measure of RDT performance, which is centrally and impartially administered and which meets the strictest standards of laboratory testing, whereas *sensitivity* and *specificity* are not standardized and their values depend closely on samples selected for the study RDT quality and storage conditions and the user's skill in preparing and interpreting test results.

# Step 2
## Estimating needs

### 2.1 Quantification

- Areas with no malaria surveillance data
- Areas with unreliable malaria surveillance data
- *Areas with reliable malaria surveillance but no reliable data on RDT consumption*
- Areas with reliable malaria surveillance and RDT consumption data

**SAFETY STOCKS**

As it is impossible to estimate requirements with complete accuracy and to be certain about the supplier's performance, a certain stock (inventory) of RDTs is needed to absorb fluctuations in supply and demand and to reduce the risk for stock-outs. As high stock levels increase inventory costs (personnel, storage, risks for spoilage, expiry and theft), most public supply systems should calculate a minimum 'safety stock'.

### 2.2 Transforming estimated needs into orders

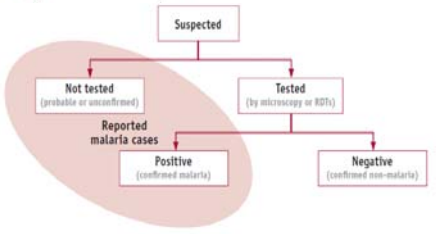


# Areas with reliable malaria surveillance but no reliable data on RDT consumption

**Recorded data:**

- total number of reported malaria cases,
- number of malaria cases confirmed by microscopy,
- total number of slides examined by microscopy for malaria,
- number of malaria cases confirmed by RDT,
- total number of malaria RDTs performed.

FIGURE 3
Relations between suspected cases that were tested (by microscopy and RDTs) and not tested (probable or unconfirmed) for malaria




**Step 1:**

Not tested (probable or unconfirmed) = reported malaria cases – positive (confirmed malaria)

Positive (confirmed malaria) = cases confirmed by microscopy + cases confirmed by RDTs

**Step 2:**

$$\text{RDT requirements} = \frac{\text{not tested + tested (by RDT)}}{\text{adjusted for completeness of reporting}} + \text{SS}$$

# Step 4
## Defining technical specifications

**Cassettes**

Example of cassette with separate wells for blood sample and buffer solution:


Example of cassette with combined well for blood sample and buffer solution:

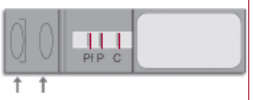

**Card**

Open card:

Closed card:

**Dipstick**

**Hybrid**




Blood sample and buffer solution wells

FIGURE 5
Schematic representation of an RDT cassette

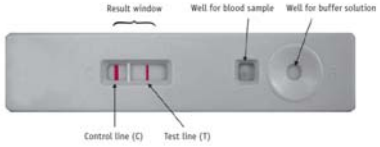
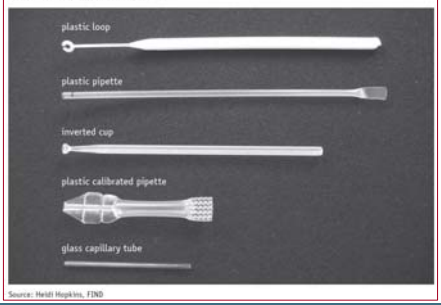



FIGURE 6
Blood collection transfer devices




Source: Heidi Hopkins, FIND



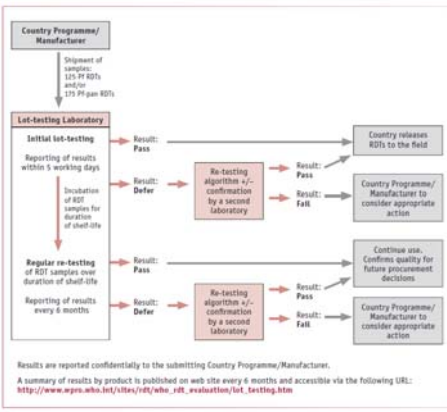
# Step 9
## Quality control by lot testing

- **Lot testing – Why?**
  - Rounds 1 + 2 results confirmed: inter-lot and inter-test performance variability
  - Provide convincing evidence to clinicians / users / regulatory authorities that RDTs are reliably working
- **Lot testing – When?**
  – pre-shipment (!)
  – post-shipment
  – post distribution
- **Lot testing – Where?**
  – Malaria RDT Quality Assurance Laboratory, Research Institute for Tropical Medicine (RITM), Muntinlupa City, Philippines
  – Laboratory of Molecular Epidemiology, Pasteur Institute of Cambodia, Phnom Penh, Cambodia

# Step 9
## Quality control by lot testing

- **How?**
  1. At least 2 weeks before the RDTs are to be dispatched for testing, send request for lot testing to mal-rdt@wpro.who.int or info@ finddiagnostics.org.
  2. Request form with instructions on sample size and shipping will be sent to you.
  3. Return completed submission form to lot testing coordinator.
  4. Send RDTs samples to the designated laboratory (approx. 125 P. falciparum-only RDTs or 175 combined P. falciparum and pan-specific (or P. vivax–specific) RDTs).
  5. Initial results will be returned to you **within 5 working days** of receipt of the test.
  6. Remaining RDTs are stored and tested every six months throughout the **shelf-life**. A report of these results is sent every six months.

FIGURE 10
Lot testing




Costs: Sending institution covers transport costs, the quality control testing is done free of charge.




The manual is available at the following link:

http://www.who.int/malaria/publications/atoz/9789241501125/en/index.html

**Thank you**