

Quality Assurance of Malaria Rapid Diagnostic Tests

Buying well and Maintaining Accuracy

Aim

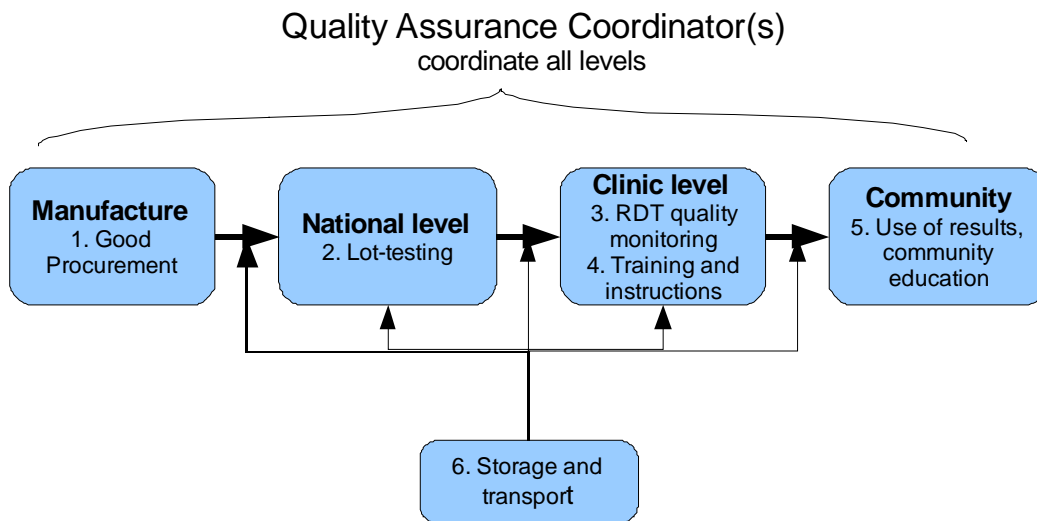
This note has been developed to update personnel coordinating malaria diagnostics programmes on current materials and recommendations of WHO regarding the use of malaria rapid diagnostic tests (RDTs), and upcoming future developments. It contains information useful for guiding procurement decisions, and for developing funding proposals and implementation plans.

Background

The introduction of malaria RDTs into control programmes is consistent with WHO recommendations that malaria case management be based on demonstration of parasites in most cases.¹ Malaria RDTs, when used well, can provide a rapid and reliable way to demonstrate the presence or absence of malaria parasites at all levels of the health service. However, evidence exists that current test accuracy in the field is variable, due to poor manufacture or exposure to high temperatures during transport and storage, and that negative results are frequently ignored by health care providers. To be effective, RDT introduction must be carefully planned, and the quality of testing ensured and demonstrated. Once this is achieved, RDT results can guide therapeutic decisions.

¹ WHO (2006). The role of laboratory diagnosis to support malaria disease management: Focus on the use of rapid diagnostic tests in areas of high transmission. Geneva, World Health Organization.

Current Recommendations



1. Planning for RDT introduction

This requires a strategic plan with clear timelines to ensure that the various components of the RDT programme are in place at the right time. A *Quality Assurance Coordinator(s)* should be designated as quality assurance coordinator to oversee the overall implementation plan and ensure that all agencies involved understand the process and their particular roles, and none are neglected. The programme budget must include a significant component for planning, training, quality assurance and logistics, in addition to procurement. An example, covering the minimum requirements, is included in Annex One.

2. Procurement

It is recommended to procure from manufacturers with evidence of quality of manufacturing, evidenced by ISO13485:2003 compliance². The WebBuy procurement list for RDTs available through the WHO procurement system (<http://extranet.who.int/newwhowebbuy/catalogues/viewCategory.asp?catalogID=13&categoryID=1054>), and the wider list of products at www.wpro.who.int/sites/rdt, are currently based on these criteria. ISO13485:2003 certification should provide evidence of consistency and quality in manufacturing, but does confirm good product performance.

An example procurement algorithm is shown in Annex Two. The steps in the algorithm should be followed sequentially, using the malaria RDT product table available at www.wpro.who.int/sites/rdt. The algorithm will rapidly reduce the list to

² Compliance to USFDA 21 CFR part 820 is similar, but clear evidence of adherence may be hard to obtain.

a short-list suitable for procurement purposes. Answers can then be approached to provide the documentation regarding the remaining specifications in Box 1.

Box 1. Selection of RDTs from an ISO13485:2003-based short-list should then be guided by the following factors:

- Plasmodium species to be detected (*P. falciparum* only, pan-specific or other species-specific).
- Sensitivity and specificity
- Thermal (temperature) stability in intended conditions of storage and use
- Ease of use
- Requirement for post-treatment testing of patients
- Cost

The manufacturer should provide:

- Evidence of viability of manufacturer
- Product support
- Sample products ...test for ease of use etc.
- Agreement for replacement of failed product
- Appropriate packaging
- A good blood-transfer device

Sensitivity and specificity are difficult to assess, as they are dependent on the parasite density and other characteristics of the population tested, on RDT preparation and interpretation, and on the quality of the reference standard. Data on test accuracy should be obtained from the manufacturer, but it should be interpreted with caution. In order to evaluate test sensitivity and specificity, lot-testing and field monitoring are essential.

Thermal stability data should be obtained from the manufacturer, and compared with conditions of intended transport, storage and use. The parasite density (antigen concentration) of the standard used to assess stability should be noted, as a heat-damaged RDT may still detect samples with high parasite density.

Staggered delivery is good policy (splitting delivery from the manufacturer into 2 or 3 batches several months apart), as it reduces the burden on central storage facilities, and allows new products to be received nearer the expected time of use, shortening storage times and effectively lengthening the shelf-life of the overall procurement.

3. Lot testing: Pre- and Post-purchase

It is recommended that all lots (batches) of RDTs be tested before deployment to the field. A 'lot' to be tested is normally defined as a production run using a particular batch of monoclonal antibodies and nitrocellulose. They are normally defined by number in this way by the manufacturer, and usually consist of 40000 to 80000 tests. Lot-testing can be done:

- (1) before purchase, directly arranged with the manufacturer and a lot-testing centre
(note: *WHO WebBuy can not arrange this*)
- (2) after purchase, before distribution to the field.

Why lot-test?

- Lot-lot variation noted in most products
- Ensure no damage during transport to country
- Need to convince clinicians / users / regulatory authorities that tests are working

Lot-testing is readily accessible now. Lot-testing capacity has been developed through a joint programme of the WHO and the Foundation for Innovative New Diagnostics (FIND), and can be facilitated by WHO. It is currently performed at two lot-testing centres in the Western Pacific Region which can test for any programme globally, and capacity is currently being developed for lot-testing in Africa and WHO will provide information on further lot testing laboratories with full contact details as soon as they will become fully operational.

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Requests for more information related to lot-testing should be made to WHO/WPRO at: mal-rdt@wpro/who.int and belld@wpro/who.int

Lot-testing is currently conducted through the WHO-FIND network at no charge, but the sending institution covers transport costs. At least 2 weeks prior notice should be given before shipping the RDT tests.

Testing is performed on a sample of about 125 *P. falciparum*-only RDTs or 175 combined *P. falciparum* and pan-specific RDTs, for each production lot in the order. The lot-testing centres follow procedures developed by WHO for this purpose³, and usually return initial results within 5 working days. Retained RDTs are then monitored every 3 months throughout the shelf-life at close to the manufacturer's recommended maximum storage temperature, and the procuring agency informed of results throughout the shelf-life. Further detail can be found at www.wpro.who.int/sites/rdt

4. Monitoring Performance in the Field

Field monitoring is difficult, partly due to the inherent problems of accuracy of field microscopy, with which RDTs must be compared. At present, the following procedure is recommended:

³ WHO (2006). The role of laboratory diagnosis to support malaria disease management: Focus on the use of rapid diagnostic tests in areas of high transmission. Geneva, World Health Organization.

- Compare RDT results with expert light microscopy. RDTs and blood films (BF) should be taken from the same patients in selected health facilities where RDTs which have undergone typical storage and distribution.
- E.g. Every month, 40 RDTs (20 positive and 20 negative) should be cross-checked against the corresponding 40 BF obtained from the same patients and examined by expert microscopist. Where >10% discordant results occur, a more detailed field evaluation should be rapidly performed or the remaining RDTs should be returned for laboratory testing (see 'lot-testing' above).
- Expert microscopy may be available at the 'sentinel' sites used for monitoring therapeutic efficacy of antimalarial medicines, or at the central/regional reference laboratory. It is important that the microscopists selected for the evaluation of RDT performance have high competency.

In addition it is important to supervise the health workers performing RDTs on a regular basis at least every 3 months in order to

- evaluate health worker capacity of interpreting a set of prepared RDTs,
- assess health worker technique in RDT preparation,
- review diagnosis and treatment records.
- ensure good blood safety practices are maintained
- ensure sufficient supplies are in place for management of malarial and non-malarial fever.

5. Training and Instructions for users

Appropriate training of health workers is needed prior to introduction of RDTs, and instructions should be clear, in locally-appropriate language, and tested. WHO and partners have developed generic job-aids and a training manual for health workers, based on trials in Asia and Africa with several partners. These materials are available in English and French, and can be adapted to other languages. Examples are downloadable from www.wpro.who.int/sites/rdt

6. Use of results and Community Education

There is wide evidence that RDT (and microscopy) results are frequently ignored when treatment decisions are made. To address this, it is essential to:

- Ensure and demonstrate the accuracy of the RDTs (through the quality assurance processes above)
- Provide management algorithms for appropriate management of parasite-negative cases (non-malarial febrile illness), and train health workers in their use
- Provide health workers with the means to manage parasite positive and negative cases appropriately
- Educate (sensitize) the community on the importance of parasite-based diagnosis.

Malaria diagnostic programmes therefore require an approach that addresses fever management, not just malaria management. It is essential to move beyond a narrow malaria-only approach to have a successful programme.

7. Storage and transport

Standard supply management procedures should be applied to minimize storage times and exposure to extremes of temperature, similar to those for the handling of drugs. These include staggered delivery of large purchases, first-expiry—first-out stock management, controlled-temperature centralized storage, and minimizing storage in peripheral facilities with no temperature control. Direct sun exposure should be avoided, and transport coordinated to minimize exposure to temperatures exceeding the manufacturer's recommended storage temperature.

Future Development

Malaria RDT Product Testing

Product testing of malaria RDTs will be underway in mid-2008. Testing will occur against a panel of geographically-diverse parasite-positive blood, and a parasite-negative panel, and include a thermal-stability test⁴. The specimen bank on which testing will be based is currently under development at US CDC in Atlanta, USA, and sample collection is underway at malaria endemic sites in Africa, Asia and the Americas. This project is a joint project between WHO/TDR and WHO/WPRO, and FIND (Foundation for Innovative New Diagnostics). The testing and dissemination of results will be overseen by WHO and results of test performance will be published in a similar manner to those for HIV, Hepatitis B and C virus, and syphilis rapid testing programmes of WHO.

Malaria RDT Prequalification

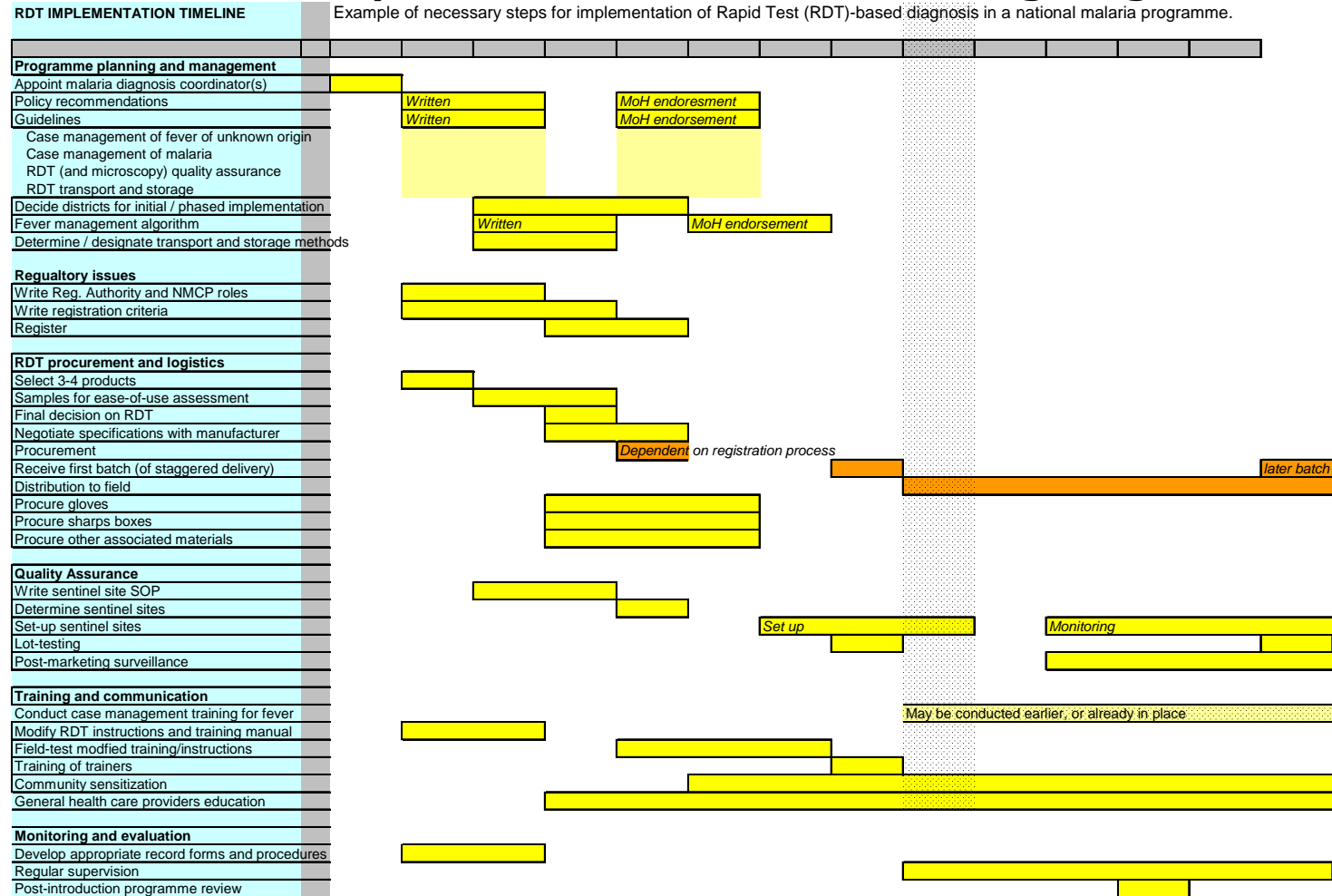
A pre-qualification programme for malaria RDTs is under development by WHO/EHT, in collaboration with WHO/GMP, WHO/TDR and WHO/WPRO. This will involve the review of documentation submitted by manufacturers, inspection of the production facilities and RDT product testing. It is expected to be in operation within the next 2 years.

Positive Control Wells

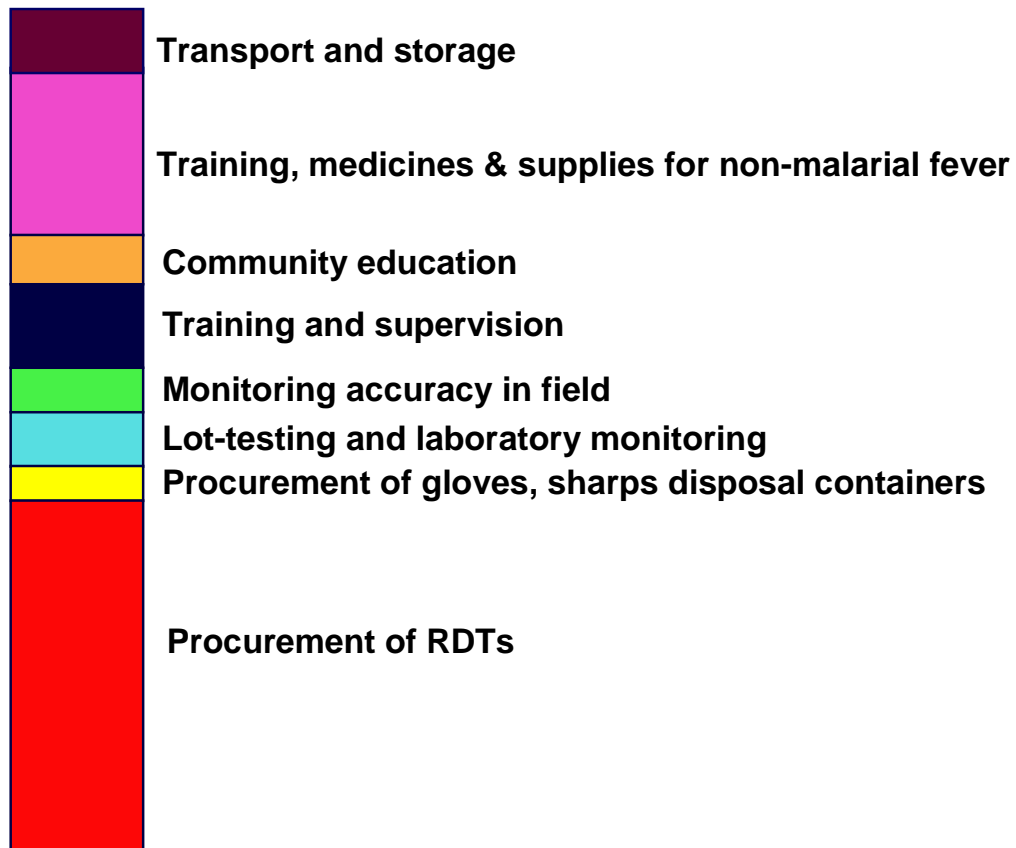
WHO is collaborating in development of stable, well-calibrated positive control wells, containing recombinant antigens and designed to allow testing of malaria RDTs at clinic or village levels. These positive control wells will enable rapid direct evaluation of RDTs performance in remote locations without the need for cross-checking against expert microscopy. In addition, a panel of wells of different antigens is also under development for standardized testing to be carried out at national level, which could have application for national regulatory testing and pre- or post-purchase lot-testing. Positive control wells are expected to be available within the next two years; until that time the following systems can be used to evaluate RDT performance: 1) WHO-supported RDT pre- and post-purchase lot-testing in qualified centres, and 2) monitoring performance in the remote areas requiring RDT comparison with microscopy.

⁴ WHO (2006b). Towards quality testing of malaria rapid diagnostic tests: Evidence and methods. Manila, World Health Organization.

Annex 1: RDT Implementation timelines and budgeting



EXAMPLE OF BUDGETING DISTRIBUTION FOR A TYPICAL RDT-BASED DIAGNOSTIC PROGRAMME



Note: The distribution of funds will vary widely depending on the level of RDT use in the health system, and the logistical and support services already in place.

Annex 2: Short-listing RDTs for Procurement

(Commence with ISO13485:2003-based product list: e.g. www.wpro.who.int/sites/rdt)

Parameter	Decision process	Decision
<p>1. Plasmodium species to be targeted</p>	<pre> graph TD A[Distinguish non-Pf from Pf or mixed?] -- Yes --> B[Combination test HRP2-pan pLDH HRP2-pan aldolase Pf pLDH-pan pLDH] A -- No --> C[Pf-only test HRP2 pLDH (may be combined with pan-specific pLDH)] </pre>	<p>.....</p> <p>.....</p> <p>.....</p> <p>.....</p> <p>.....</p>
<p>2. Expected areas of use</p>	<pre> graph TD A[Store and use in tropical/hit environment without] -- Yes --> B[High-stability test Specified temperature e.g. ≥35°C] A -- No --> C[Storage temperature less critical Accept <35C specified storage] </pre>	<p>.....</p> <p>.....</p> <p>.....</p> <p>.....</p> <p>.....</p>
<p>3. Likely clinical scenarios</p>	<pre> graph TD A[Likely to use for re-testing soon after treatment / treatment-monitoring] -- Yes --> B[Target non-persistent antigen pLDH-detecting for P. falciparum] A -- No --> C[Antigen persistence not critical HRP2 or pLDH for P. falciparum] </pre>	<p>.....</p> <p>.....</p> <p>.....</p>
<p>4. End-user</p>	<pre> graph TD A[For use by health workers outside medical laboratories] -- Yes --> B[Simple format, all-inclusive Cassette design Lancet, swabs etc included in package] A -- No --> C[Design less critical Include dipsticks Test-only packaging] </pre>	<p>.....</p> <p>.....</p> <p>.....</p>
<p>5. Other considerations: Box size: How many fever cases expected in 3 months (if less than one box, request reduced box size)</p>		<p>.....</p> <p>.....</p> <p>.....</p>
<p>Next Step: Develop short-list of Suitable RDTs High-light tests on WHO RDT Website list (ISO13485-accredited manufacturers, or WebBuy list if procuring within WHO system). Sometimes preferences will be incompatible, in which case follow the general priorities of the numbered order above.</p>		

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Choosing specific products from the short-list

If procuring through WebBuy, some of the above information will already be available)

1. Contact Manufacturers

Request:

1. Price (include delivery to country, and staggered delivery in 2-3 batches over 12 months)
2. Request heat stability data as evidence of manufacturer's stated storage temperature and shelf-life.
3. Request sample of product to assess format, ease of use, compatibility of other materials with health system requirements



2. Assess other experience

If possible, obtain written assessments of field experience from other countries / programmes that have experience in using the product.



Make preliminary procurement decision, then...



3. Options to consider to improve implementation

1. Negotiate replacement of product if fails lot-testing after delivery by method approved by manufacturer / WHO-coordinated laboratory.
2. Develop appropriately-formatted instructions in appropriate language consider inclusion in boxes at manufacturing site.
3. Negotiate delivery dates for staggered delivery to reduce in-country storage times.