

Guidelines for Bivalent RDT

Introduction

At present about 100 million fever cases suspected to be malaria are screened for malaria annually under the National Vector Borne Disease Control Programme. In addition to that, 5% of negative slides (about 5 million) and all positive slides (1.5 million) are to be cross checked for quality control. Due to the shortfall of technicians there is delay in reporting the results. Use of Rapid Diagnostic tests (RDTs) for detection of *P. falciparum* (Pf) cases was introduced in the programme during 2004-05 and at present around 14 million RDTs are being procured and used annually.

With the present *Pf* specific RDT there is no reduction in the load of microscopy as all slides for all patients with negative RDT result (around 97% of total slides) are to be sent for microscopy to detect/ rule out *P. vivax* (Pv). Although *Pv* infections usually do not result in fatalities but some mortalities due to *Pv* especially in children are being reported from various parts of the country during recent times. Therefore it has been felt that Introduction of bivalent RDT will be useful in early treatment of *Pv* in areas where microscopy results get delayed.

In the prevailing situation at present, the average efficiency of microscopy may not be more than 60% in many microscopy centers. Microscopy cannot be replaced with RDT at any circumstance and maximum scope for RDT is estimated to be around 40 million (40%) annually and remaining 60% cases will need microscopy for diagnosis. The bivalent RDTs would supplement and help in immediate diagnosis and prompt treatment in areas from where microscopy facility is not readily accessible; but can never replace microscopy which is still considered the gold standard for diagnosis of malaria.

The matter was deliberated by the Experts Group on Chemotherapy and Diagnosis on 18-02-2011 and the following recommendations were made:

- Introduction of bivalent RDTs in the programme right away without waiting for the field trial which may take a minimum of one year or more. It was also opined that at present it may be used in high malaria endemic areas where *Pf* specific RDT is already being used.
- The bivalent RDTs would primarily be used in the remote and hard-to-reach areas where microscopy results cannot be made available within 24 hours. However, RDTs may also be used in PHCs, secondary and tertiary level facilities, for patients arriving in odd hours when the laboratory technician is not immediately available and in emergencies like dealing with severe malaria cases.
- Regarding the criteria for selection of RDTs, the recommendations are as under:

- i. For Pf: Sensitivity and Specificity should be minimum 95% at parasite density level of 200 asexual parasites/ul of blood
 - ii. For Pv:
 - Sensitivity: $\geq 75\%$ at density of 200 parasites/ul
 - Specificity : $\geq 90\%$
- Type of RDT- Only Histidine-Rich Protein 2 (HRP2) and Parasite lactate dehydrogenase (pLDH) based RDTs to be used and not aldolase based ones.
 - In areas where bivalent RDT is introduced, operational research would be conducted and data thus generated will be analyzed for further expansion of bivalent RDT use in the country. The research protocol will include both HRP2 and pLDH based kits in areas with high and low endemicity and in high and low parasitaemia cases.
 - The microscopy centers, with the reduced load, would be strengthened by capacity building of the laboratory technicians and better logistic support so as to provide quality microscopy services.

Accepting the recommendation of the committee, the Bivalent RDT is being introduced in the programme with the procurement cycle of year 2012.

Guidelines for its use:

A patient with fever and no other obvious cause of fever is considered a case of suspected malaria. Any Community health volunteer, health worker or health professional observing a case of suspected malaria must immediately initiate a diagnostic test by

1. Microscopy of blood for malarial parasites and/or
2. Rapid Diagnostic Test

Under the programme Slide Microscopy for Malaria is the standard diagnostic tool & wherever a microscopy result **can** be made available within 24 hours, microscopy will be maintained as the only routine method for diagnosis of malaria.

Due to problems of non-availability of Lab Technicians at certain block PHCs & the huge time lag between the slide collection & reporting of results, especially from remote & inaccessible areas, the microscopy result may not be made available within 24 hours. In such areas also, RDTs will be supplied and used for diagnosis. The criteria for selection of these villages (or sub-center areas, where village data is not available) are:

- Pf % > 30 and SPR > 2%:
- Consistently high API (>2) and deaths due to malaria are reported
- Inaccessible areas – i.e. cut off during transmission season, areas with limited road and public transportation facility.

RDTs will be used in PHC and other health facilities only in emergencies for treatment of severe and complicated malaria requiring immediate medical attention in the absence of the laboratory technician (LT).

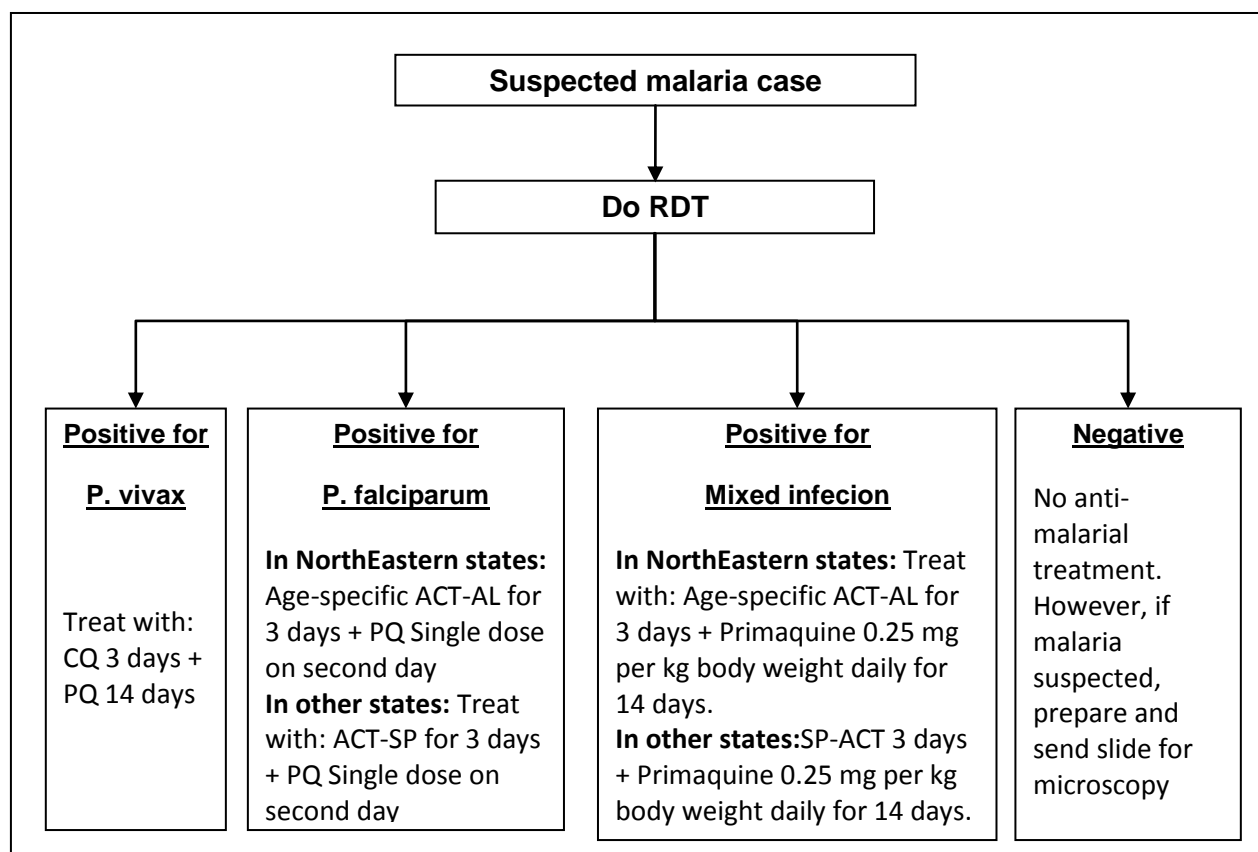
The limitations on the deployment of RDTs, are meant to avoid wastage of these products. In areas, where the risk of malaria is very low, it is not cost-effective to test every patient with fever.

However, in such areas, a small number of RDTs should be available at health facilities to test fever patients reporting during the emergency with a very high suspicion of malaria such as those, who have recently stayed overnight in an endemic area.

Steps for the use of bivalent RDT

A patient with fever and no other obvious cause of fever is considered a case of suspected malaria. Any Community health volunteer, health worker or health professional observing a case of suspected malaria must immediately initiate a diagnostic test as per the guidelines.

Where microscopy result is not available within 24 hours and Bivalent RDT is used



Note: if a patient has severe symptoms at any stage, then immediately refer to a nearest PHC or other health facility with indoor patient management or a registered medical doctor.

Note: PQ is contra-indicated in pregnancy and in children under 1 year (Infant).

ACT-AL - Artemisinin-based Combination Therapy- Artemether - Lumefantrine

ACT-SP- Artemisinin-based Combination Therapy (Artesunate+Sulfadoxine-Pyrimethamine)

CQ - Chloroquine

PQ - Primaquine

- An RDT is done in front of the patient and a slide is taken. The bivalent RDT detects *Pv*, *Pf* as well as mixed infection. If it is positive, the patient is treated for falciparum or vivax malaria based on the diagnosis and the slide is discarded in order to reduce the load on the microscopy services.

- In the bivalent RDT if line for *Pf* is found present then it is a case of *Pf* and accordingly the full course of ACT for three days and Primaquine on day 2 (second day) is to be given.
- If the line for *Pv* is present, then it is a case of *P vivax* and a full course of Chloroquine for three days and Primaquine for 14 days is to be ensured.
- If both the lines for *Pf* and *Pv* are present, then it is a case of mixed infection and the treatment of mixed infection i. e. ACT for three days and primaquine for 14 days is to be given.
- If the RDT is negative, (i.e. only control line is present) then the slide is discarded.
- If no other cause can be found and the clinical suspicion is high (e.g. intermittent fever with rigors and sweats), the test should be repeated after about 24 hours and special efforts should be made to obtain the microscopy result rapidly.
- Some slides may also need to be preserved for cross checking the results as per the Quality Assurance Guidelines.

However, the worker/ health personnel should refer the product guidelines for any product specific instruction before using it.

Rapid Diagnostic Tests

It should be noted that these tests have a short shelf-life and that they may deteriorate at high temperatures. Some manufacturers are now indicating that their product has a longer shelf-life. Although this is encouraging, malaria control staff and medical officers should manage rapid diagnostic test kits (RDKs) under the assumption that the shelf-life is 24 months.

Interpretation of rapid diagnostic tests

HRP2-based tests for *P.falciparum* detect a circulating antigen excreted by asexual plasmodia. The tests have a sensitivity of about 95%, when the asexual parasite density is above 200/ μl . Malaria patients are rarely symptomatic at lower densities.

If a suspected malaria patient has a negative RDT, it can therefore be assumed that the patient does not have malaria and another cause of the fever should be sought. If no other cause can be found and the clinical suspicion is high (e.g. intermittent fever with rigors and sweats), the test should be repeated after about 24 hours and special efforts should be made to obtain the microscopy result rapidly.

HRP2 antigen can persist for up to 4 weeks after clearance of asexual parasitaemia through treatment. False positive tests are therefore common, especially in patients with a recent history of treatment. RDTs should therefore **not** be used for following up patients after treatment. If a patient, who has been treated, is febrile within one month after the treatment and the RDT is positive, the patient **may** have malaria. If possible, the diagnosis should then be confirmed by microscopy.

The above rules for use of diagnostics should be applied at all levels of care and in passive as well as active case detection.

Calculation of the annual requirement of RDT

S.No.	District	No. PHCs where RDTs are to be used in emergency hours	No. of sub-centre areas with SPR >2% and API>2 & Pf > 30% & no microscopy result within 24hr.	No. of blood examinations in those sub-centre/ PHC areas last year (A)	Expected RDT requirement in remote high risk areas and PHCs [Ax 0.4 x 1.25] (B)	RDTs for buffer stock and distribution to other areas: [B x 0.25] (C)	Total annual RDT supply [B+C]
1							
2							
3							
Total							

- Villages planned to be equipped with RDTs should have trained ASHA/ CHVs (including Angan Wadi Worker)
- The number of (blood) test examinations is estimated by adding 25% to the 40 % of number of blood examinations during the last completed calendar year, because RDTs may attract additional patients.
- If possible, a buffer stock of approximately 25%, depending on the availability of supplies is added, to cover needs in other areas and health facilities, where impending outbreaks may be suspected or where individual patients may be considered as highly suspect of malaria on account of symptoms or travel history, or where microscopy may be temporarily unavailable and to provide a reserve for supplies to the eligible areas.
- Procurement of RDT is done centrally (mostly for the project states under EAC). However, the state may be required to procure buffer stock of 25 % if the central procurement is delayed due to any reason.

Guidelines for Proper Storage of Drugs and Commodities

The main purpose of storage is to protect the quality of products and its packaging throughout the supply chain and make products available for distribution. The brief guidelines for storage of drugs/commodities are mentioned below:

1. Clean and disinfect the store room regularly and monitor the storage conditions
2. Clean receiving, storage, packing areas and remove the garbage and also keep the stores away from rodents, insects and termites
3. Safely handle the health commodities while loading and unloading from the transport vehicle
4. Clean bins, shelves and cupboards, if needed and
5. Store supplies in a dry, well-lit and well ventilated store room and out of the direct sunlight
6. Ensure adequate ventilation and temperature control (not more than 40⁰ C).
7. Provide the rack storage system in such a way so that gang ways may be created for easy movement of materials and personnel handling the store
8. Stack cartons in steel racks/slotted angles and at least 10 cm(4 inch) off the floor, 30 cm (1ft) away from the walls and other stacks and no more than 2.5 m (8ft) high

9. Store supplies in a manner that is accessible for FEFO, counting, and general management. Use First Expiry First out (FEFO) principle. Please issue the drugs which are going to expire first.
10. Store medical supplies separately, away from insecticides, chemicals, old files, office supplies, and other materials.
11. Arrange cartons so that arrows point up, and ensure that identification labels, expiry dates, and manufacturing dates are visible.
12. Monitor store security and safety to avoid theft/pilferage
13. Secure store room from water penetration and from any seepage in the walls, roof, doors & windows, especially during rainy season
14. Monitor product quality (visually inspect commodities and check expiry dates) and physical verification of quantities
15. Ensure that fire safety equipment (fire extinguisher) is available and accessible and that personnel are trained to use it.
16. Ensure fire proof electrical fittings and appliances for any fire due to short circuit and keep the stocks away from the electrical sockets
17. Separate damaged and expired stocks from the usable stock and move the expired stock to secure area and dispose of these products without delay as per the established procedure
18. Monitor stock levels, stock quantities and safety stocks and update stock ledger/records regularly and maintain the files safe custody.

Quality Assurance of RDT

Internal Quality Control (IQC)

The Internal Quality Control starts with proper shipment and storage of the kits/samples. The DMOs should ensure that the consignee lists are prepared before shipment. The principle of first-expiry-first-out should be followed in utilizing the kits. RDTs supplied by NVBDCP (though stable at temperatures up to 40°C), should however be kept in a cool, dry place away from direct sunlight. Care should be taken that the kits are at a considerable height from the ground away from dampness. The storage should be protected from rodents, fire, water and high temperature. IQC should be a part of training of ASHA, MPWs and ensure its adherence during supervisory visits by health supervisors, MTS, DMO.

External Quality Assurance (EQA)

An important component of the EQA scheme is the development and use of Quality Control (QC) panel to test the threshold sensitivity of RDTs to determine if deterioration of RDTs has occurred. The method followed to develop QC panel is preparation of antigen-based or parasite-based samples. Malaria parasites with parasite density sufficiently high are used for preparation of QC panel for testing malaria RDTs. Malaria

RDTs are designed for use with fresh human blood. QC samples should therefore mimic fresh blood infected with wild parasites as closely as possible.

QAP for malaria RDTs also aims to ensure high accuracy of tests in the hands of end-users. Besides quality, this programme also aims to monitor technical standards of the RDTs and processes to minimize environmental impacts.

i) Lot / batch Testing of RDT kits using QC samples

The sensitivity of malaria RDTs is dependent on several factors and these factors are subject to deterioration in adverse transport and storage conditions. The rates of deterioration and their effect can vary between products. Hence, it is essential to assess the quality of the RDTs at periodical intervals with known low and high positive samples. This would be achieved by lot and batch testing of the procured kits.

From each RDT lot, 13 kits would be drawn and tested using positive (low and high parasitaemias) and negative controls for immediate QC. For long term quality assurance, 28 kits would be drawn in four lots depending on the expiry date of the kit (e.g. if expiry date is around one year, seven kits would be drawn every 3 months). For this, Manual for Quality Assurance of Malaria Diagnostic Tests by the NVBDCP would be strictly followed. The tests would be carried out at the in the designated laboratories. At the periphery, DMOs would collect from health facilities and ASHAs 13 randomly selected kits and send to the linked SRLs for QA testing.

ii) EQA of the RDTs used by health workers at periphery

Once RDTs are supplied to the states; a sample would be drawn and tested for its quality from various levels. The District Malaria Officers would collect RDT samples from the periphery and send the same to SRL. Few kits would also undergo a temperature sensitivity test.

The District Malaria Officer would monitor the process of QA at peripheral levels i.e. at the lever of ASHA and health workers apart from PHCs/CHCs to determine any deterioration in the kit. Both immediate and long term QA will be performed with the RDT kits supplied to the periphery. It will be the responsibility of the DMO to pick up 2 samples of different health facilities/ASHA to check the sensitivity and specificity of RDTs on quarterly basis by selecting the villages randomly.

The DMO would collect information on lot number and batch number of the consignment at the time of distribution. He would retain randomly 14 kits out of the entire lot to send seven of them to the SRL. After 3 months randomly he would select some PHCs, out of which from one sub center he would pick up one RDT. The process would be repeated to collect total seven RDTs from different sub centers after every three months. The next batch of seven RDTs would be collected from different centers at an interval of 3 months. The process of QA will be continued till the expiry period as mentioned on the kits by the manufacturer (e.g. if expiry date is 12 months from the date of manufacturing and consignment is received after 3 months, than on receipt the 1st round of QA, thereafter 2nd, 3rd and 4th round should be carried out). The Vector Borne Diseases Consultants and Malaria Technical Supervisors/ Technical supervisor-VBD (TS-VBD) will also be actively engaged in the QA programme.

Abbreviations

ACT	Artemisinin-based Combination Therapy
API	Annual Parasite Incidence
ASHA	Accredited Social Health Activist
CHV	Community Health Volunteer
DMO	District Malaria Officer
EAC	Externally Aided Component
EQA	External Quality Assurance
FEFO	First Expiry First out
HRP2	Histidine-Rich Protein 2
IQC	Internal Quality Control
LT	Laboratory Technician
NVBDCP	National Vector Borne Disease Control Programme
Pf	<i>Plasmodium falciparum</i>
PHC	Primary Health Center
pLDH	Parasite lactate dehydrogenase
Pv	<i>Plasmodium vivax</i>
QA	Quality Assurance
QAP	Quality Assurance Programme
QC	Quality Control
RDK	Rapid Diagnostic test Kits
RDT	Rapid Diagnostic Test
SPR	Slide Positivity Rate
SRL	State Reference Laboratory
TS-VBD	Technical supervisor-VBD