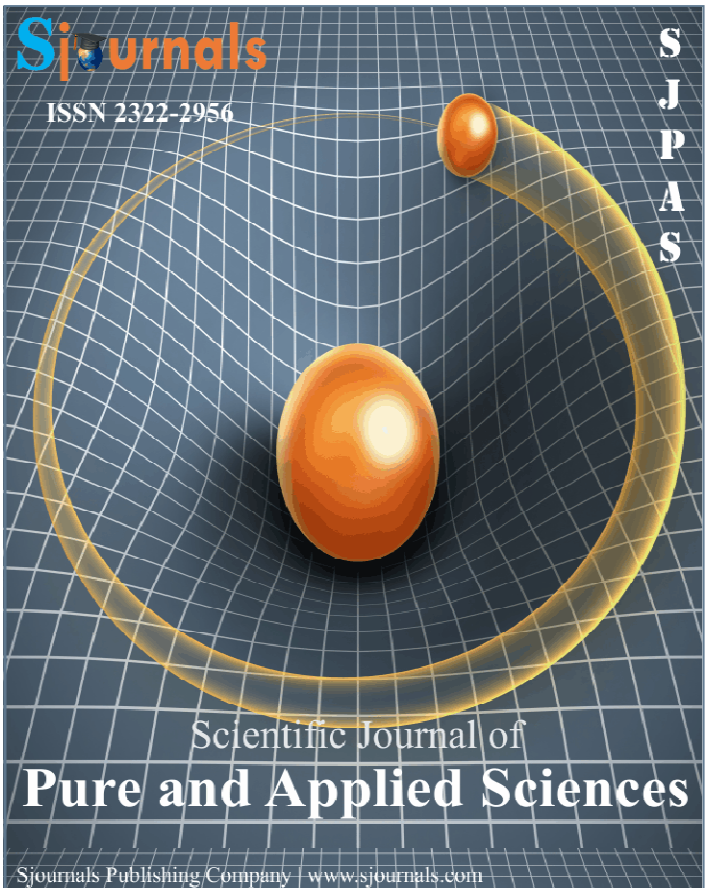

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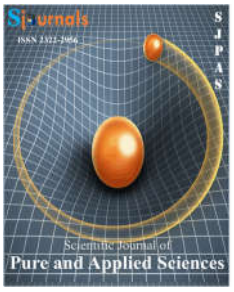

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Review article

Importance of quality assurance testing of malaria rapid diagnostic test in the case management of malaria

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ABSTRACT

Prompt and rapid diagnosis of malaria has gained importance in health programmes in endemic countries, and recognition of the importance of early, correct treatment to the reduction in malaria morbidity and mortality. Blood-based diagnosis using lateral-flow immunochromatographic tests, commonly called rapid diagnostics tests (RDTs), offer great promise in extending rapid diagnosis to areas where traditional microscopy is not accessible. Large-scale operational use has raised questions about the accuracy of current RDT technology in tropical conditions. As utilization of RDTs has increased rapidly in the last few years, there is a clear and urgent need to address issues on quality performance and appropriateness of use, particularly in remote endemic areas. The need for Quality Assurance (QA) systems to maintain the quality of microscopy diagnosis of malaria is well established but the extent of implementation varies widely. Quality assurance process must become an integral part of RDT budgets, procurement and implementation plans. Responsibility for overseeing QA processes, extending from post purchase testing of RDTs to training and supervision of users and control of storage and transport, should be clearly defined and coordinated from a central level. A system of regional and referral laboratories, based on standard operating procedures would test RDTs after purchase

and for the duration of shelf-life using quality control (QC) panels prepared from wild-type parasites. The use of positive control wells (PCW) containing recombinant antigens would assist in assuring the performance of RDTs in the field and this would assist in the parasite-base confirmation and in the case management of malaria. Quality assurance processes must be transparent, and good communication with manufacturers and end-users during QA development is necessary.

1. Introduction

Malaria Rapid Diagnostic Tests (MRDTs) are lateral-flow immunochromatographic devices based on binding of parasite antigen in host blood (WHO, 2013). Like other biological tests, MRDTs are degraded by heat and moisture and gradually deteriorate with time, even in ideal conditions. However, poorly controlled transport and storage conditions, and infrequent re-supply, necessitate a high level of reliability and stability.

Variation in MRDT accuracy in published trials and operational experience underline the need for an accurate, transparent system for monitoring the accuracy of MRDTs after release by the manufacturers. The development of a comprehensive quality is maintained reducing the likelihood of misdiagnosis and maintaining confidence of health service providers and consumers. Malaria rapid diagnostic tests has led to great improvement in the early recognition and management of both malarial and non-malarial fever, through demonstration of antigen specific for malaria parasites in the host blood. Parasite-based diagnosis of malaria is important as rising resistance of malaria parasites drugs has led to rising use of artemisinin-based combination therapy (ACT) and other drug combinations (WHO, 2013).

Malaria RDTs have a major role in malaria management, particularly in providing parasite-based diagnosis in remote locations where microscopy-based diagnosis is unavailable. Like other diagnostic pathology tests, various conditions of manufacture, transport, storage and use may impair their accuracy. The introduction of malaria RDTs into control program is consistent with WHO recommendations that malaria case management be based on detection of parasites in all cases. 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 transportation 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.

Most manufacturers recommend that MRDTs be stored between 2 and 30°C (Jorgensen et al., 2007). However, the use of RDTs in remote areas entails storage in tropical and subtropical conditions which may be outside the storage temperature of the MRDT. An ideal MRDT should be able to tolerate temperatures of at least 40°C, with peaks of 50°C, under storage for up to 2 years (WHO, 2000; WHO, 2009). There are limited data on the stability of many MRDTs under such conditions at present, and more extreme conditions may occur temporarily during transport. The stability and sensitivity of products may also vary between lots. It is important that users minimize exposure to high temperatures, and to monitor the performance of each lot (WHO, 2004; WHO, 2009). Transportation of MRDTs from the manufacturer, and road transport within the country is very important in ensuring the preservation of the integrity of the MRDTs for better performance. Prolonged exposure to high temperature and humidity will rapidly degrade RDTs, and may occur when exposed to intense heat (above 30^{o}C and after removal from the envelope or if the envelope is damaged (Chiodini et al., 2007).

The aim of QA is to provide reliable, relevant and timely test results that are interpreted correctly thereby increasing efficiency, effectiveness, enhancing patient satisfaction and decreasing costs brought about by misdiagnosis. Quality control describes all the activities taken by a laboratory to monitor each stage of a test procedure to ensure that tests are performed correctly and are accurate. Quality Control must be practical, achievable and affordable. Quality Control is a system of laboratory based assessment and monitoring the performance of MRDTs throughout their shelf-life and ensuring appropriate standard operating procedures (SOPs)

are followed. Quality Control indicates whether a test run is valid as well as cross-checking a routine test for accuracy (Jorgensen et al., 2006).

The invention of positive control wells (PCW) which is composed of recombinant antigen at concentrations intended to give a positive result. This would enable village health worker or care provider to test an MRDTs from any box before use, ensuring that the kit has not degraded during storage and transport, thereby boosting confidence that the results of test can be used to initiate therapy. This development promises to greatly improve on the current need to perform comparative microscopy at sentinel sites to monitor MRDT field performance and this would the boost the current policy on parasite base confirmation and assist in malaria case management. (Perkins and Bells, 2008; Gersti et al., 2010).

Quality assurance process for MRDTs is aimed to ensure high accuracy of tests in the hands of end-users for an effective malaria case management. Manufacturers of RDTs should be trained on the importance of producing standard MRDTs and should be encouraged to submit their product to WHO for product and lot testing. Manufacturers should also produce MRDTs under Good Manufacturing Practices (GMPs). The absence of quality assurance MRDTs would lead to lack of confidence on the RDT by MRDTs users and over-diagnosis and over prescription of antimalarials. Health workers using MRDTs should be regularly trained and monitored especially on the preparation and interpretation RDTs results (WHO, 2010). The objective of this seminar is to review the importance of malaria RDTs quality assurance testing in malaria case management.

2. Quality assurance of malaria rapid diagnostic test (MRDTs)

The adoption and use of expensive artemisinin-based antimalarial therapies in the past few years is unprecedented but has not been matched by a similar increase in parasitological confirmation of malaria diagnoses. Targeted treatment is important, not only to limit unnecessary dispensing of antimalarial treatment but also to allow judicious use of these precious, life-saving medicines, for which the supply of raw materials is decreasing because of reduced cultivation of *Artemisia annua* (WHO, 2009).

Quality assurance is defined as a total process, both in and outside the laboratory including performance standards, good laboratory practice (GLP) and management skills to achieve and maintain a quality service and provide for continuing improvement. The purpose of QA is to provide reliable, relevant, timely test results that are interpreted correctly thereby decreasing costs brought about by misdiagnosis (WHO, 2008). Over the past several years, a QA programme for MRDTs is being used in the public sector by WHO-FIND. These activities are intended to address uncertainties both about the quality of manufacturer as well as the stability and performance of MRDTs post-purchase (WHO, 2003; WHO, 2008).

It is crucial that the accuracy and stability of malaria RDTs are monitored at every step in the process, from kit manufacture and distribution through to end use. Initial requirements include product testing to demonstrate performance characteristics of antigen detection and specificity, test stability and ease of use. Subsequently, post-purchase lot testing is required to ensure that the delivered product is consistent with these established performance characteristics. Finally, safeguards are required to ensure that users are well trained and competent in performing and interpreting RDT assays. At every stage, RDT stability under the relevant storage and transport conditions must be monitored (Bell et al., 2006).

A system for checking the continued accuracy of diagnostic services is essential in any large programme, determining treatment for a severe disease. Quality Assurance (QA) should be an integral part of MRDT budget and implementation plan in the same way that it forms an important part of a microscopy-based program. This should extend from testing at the time of purchase to testing and supervision at a peripheral level, and include monitoring of transport and storage. Responsibility for overseeing QA processes should be clearly defined and co-ordinated from a central level (Tavrow et al., 2000).

One aspect of the QA program involves assembling a restricted list of high-quality RDTs for purchase through the public sector. To be among the selected RDT list, tests must be manufactured under ISO-13485: and must show good performance when tested against a panel of reference materials that contains cultured parasites, recombinant proteins, and wild parasites and then diluted to fixed and clinically-relevant concentration of parasites. The results of MRDT, that pass this testing guide the procurements of MRDTs, only those tests showing good performance and temperature stability (WHO, 2008; Jorgensen et al., 2008). The second part of the QA programme requires countries or agencies purchasing MRDTs for public sector use to submit samples of purchased lots for testing after arrival of the products. This ensures that the lot purchased meets performance and quality

standards, and the MRDTs maintain accuracy despite temperature and humidity stresses encountered during shipment (WHO, 2008). With this capacity end-user will be assured of receiving good quality MRDTs.

The third arm of the WHO/FIND QA process for MRDTs is the provision of positive control wells (PCW), composed of recombinant antigen at concentrations intended to give a positive results that should allow the village health worker or care provider to test an MRDTs from any box before use, ensuring that the kit has not degraded during storage and transport, and boostering confidence that the results of testing may be used to direct therapy. This development promises to greatly improve on the current need to perform comparative microscopy at sentinel sites to monitor MRDT field performance (Perkins and Bells, 2008).

The World Health Organization-Foundation for Innovative New Diagnostic (WHO-FIND) MRDT evaluation programme has commenced a product testing programme to assess the performance of MRDTs product lots under ideal conditions submitted specifically by manufacturers for this purpose. QC testing serves as a guide for MRDT procurement. In view of the implications of impaired sensitivity to case management, it is vital to have a mechanism in place to ensure continued adequate performance of the tests after delivery of future production lots to countries. QC testing includes a reliable system for laboratory-based assessment of performance on delivery and throughout the expected shelf life of the tests. The World Health Organization (WHO) recommends that MRDTs be implemented, with a comprehensive quality control strategy (WHO, 2005). Firstly, MRDTs should be purchased from a manufacturer that follows good manufacturing practices (GMP). Secondly, each lot of MRDTs should be tested on arrival in the country of use to ensure that the tests were not exposed to extreme temperatures or other conditions that may affect RDTs performance.

The drive towards malaria elimination has increased the need for broad use of quality assured diagnostics for malaria, and possibly the development of novel assays to address specific needs such as the sensitivity at low parasitaemia to detect reservoirs. The imperative for parasitologic diagnosis will be increased when malaria incidence falls, and in cases where presumptive treatment of fever with antimalaria drugs is ineffective and even harmful in the vast majority of cases (Richter et al., 2004).

Mapping malarial cases is critical to understanding the effectiveness and impact of different control policies that are being implemented. Though this is currently done through testing at sentinel sites or in large population-based surveys, much more accurate and real-time infection can be gathered through the development of reporting systems that capture the results of MRDT testing at village level. Currently, very few MRDT results are recorded and translated back to centralized levels of the health system in a way that could serve surveillance needs (Wanji et al., 2008).

3. Technical aspects of testing malaria RDTs

Malaria RDTs are immunochromatographic lateral flow devices that detect parasite antigen. Capture of dye-labelled 'signal' antibody-antigen complex by a fixed 'capture' antibody produces a visible line on a nitrocellulose strip, signifying a positive test result. Different products target various antigens specific to plasmodia. Blood, product reagent and labelled antibody-antigen complex are drawn along the nitrocellulose-fibre strip by capillary action and flushing with a reagent /buffer solution. Performance of MRDTs is therefore dependent on several factors, including the rate of flow of blood along the nitrocellulose strip, the adherence of capture antibody (Ab) to the strip, ability of the Ab to bind antigen (Ag), and the integrity of the signal Ab-dye conjugate. All these factors are subject to deterioration in adverse transport and storage conditions, and rates of deterioration and their effect on outcomes can vary between products (Rennie et al., 2007).

The relationship between antigen concentration and parasite density can vary with the degree of sequestration of parasites, the stage of parasite and the persistence of antigen after reduction or elimination of the parasite population (Baker et al., 2005). The antigen concentration of a given sample with a given parasite density may significantly vary from another sample of similar parasite density. Therefore, the preparation of QC samples must take this fact into account. This is the reason why wild parasites rather than cultured parasites are used for preparing the QC samples, as the relationship between cultured parasite density and antigen concentration of the culture medium is likely to vary significantly from that expected *in vivo* (WHO, 2008). Malaria rapid diagnostic tests are designed for use with fresh human blood. QC samples should therefore mimic fresh blood infected with wild parasites as closely as possible. Parasite QC samples are derived from fresh blood and prepared and stored in a manner designed to minimize loss of antigen or other changes that may affect MRDTs performance (WHO, 2009).

Variation in the structure of some parasite antigens affects binding to antibody. This variation should be taken into account when interpreting failure of tests against samples with low parasite density, and in the choice of QC samples to verify these results (Gamboa et al., 2010).

4. Quality assurance of MRDTs from the manufacturer's end

In addition to considerations of sensitivity, species of parasite detected and cost, it is important for potential purchasers of MRDTs to have an idea of the quality of manufacturing processes (e.g. ISO certification, GMP procedures). The long-term viability of a company will determine the ability to replace product should the received lot fail, and to provide long term supply of a product to minimize the need to re-train end-users (WHO, 2008).

Apart from consideration of the technical aspects of MRDTs, the major issues to be considered before an MRDT can be recommended for procurement are; purchasers should request for evidence of GMP/ISO certification, accelerated heat stability data on each lot and real-time heat stability data on each product, evidence of successful operational use or good quality field trial data on the product. long-term viability of manufacturer (staff size, financial statement and/or track record) changes in raw materials and format of products should be clearly noted on the product label and parasite-base QC panel used for WHO-coordinated QC should be available to manufacturers. These should be from geographically-diverse areas (WHO, 2007; WHO, 2010).

The number of manufacturers and rate of change of products, the diversity of natural regulatory background and the potential costs make monitoring of manufacturing standard by WHO impractical at present. Approval of manufacturing facilities through a process similar to that used for drug manufacturing may be appropriate for review in the future. Manufacturers of MRDTs currently use a number of standards during internal quality assurance processes. It would benefit manufacturers if a panel of quality control samples were available for testing products. The QC panels could be prepared by regional laboratories as part of post-manufacturing quality control coordinated by WHO. Pre-release QC testing of RDT lots would then be performed using the same samples used for post-release testing by purchasers/users in QC laboratories (WHO, 2008; 2013)

Real-time data on stability of MRDT products up to the expiry date are required as evidence of stability of MRDTs. While all products are expected to have real-time stability data. Accelerated (lot) data must be requested as part of the tendering process. Accelerated data can be used to estimate real-time stability (McMorrow et al., 2008). Changes in the format or raw materials used in RDTs (for example; different sources of monoclonal antibodies or nitrocellulose) must be indicated by appropriate changes in labeling to clarify that the product is different from previous versions.

Inadequate labeling of MRDTs have been reported such as absent or insufficient labels on individual RDT envelopes. Product type, lot numbers and expiry dates should be clearly labeled on all packaging including RDT envelopes, to allow identification of individual RDTs to QC results (WHO, 2008). Inadequate labeling prevents identification if boxes are shared or tampered with.

4.1. Importance of quality assurance

Variation in RDT accuracy in many published trials and operational experience, underline the need for an accurate, transparent system for monitoring the accuracy of RDTs after release by the manufacturer. The development of a comprehensive quality assurance scheme is essential to ensure that test quality is maintained, reducing the likelihood of misdiagnosis and maintaining confidence of health service providers and consumers. With time, this scheme will provide standard evidence to test performance to guide purchasing and development.

Malaria RDTs are affected by various conditions of manufacture, storage and use that can impair their accuracy and reliability. The global initiative to scale-up the introduction of RDTs to aid in the management of malaria, especially in locations where laboratory-based diagnosis is unavailable, therefore requires a system in place to ensure that service quality is guaranteed (Jorgensen et al., 2006). This is increasingly important with the advent of combination therapies and their higher associated costs. The aim of Quality assurance process for MRDTs is to ensure high accuracy of test in the hands of end-users. This will include both monitoring of the technical standard of the MRDTs, processes to minimize environmental hazards, training and monitoring of preparation and interpretation of the MRDTs by the end-users (Lon et al., 2005; Jorgensen et al., 2006).

Microscopy is used to conduct quality control of MRDTs during routine implementation. Quality control of MRDTs based on poor quality blood smear staining may impede reliable measurement of sensitivity and specificity and undermine confidence in the use of MRDTs (McMorrow et al., 2008). Collecting blood smear for 1-2 days per

month at health facilities performing MRDTs might provide sufficient quality control, but remains labor intensive. Additional training also had little impact on MRDT performance. Further WHO recommendation for post-deployment quality control include sentinel site surveillance and teaching problem solving skills to health workers when MRDTs are not performing well. Sentinel sites surveillance would only provide an assessment of RDT quality at a few centers, which might be improved by staff that have higher levels of training or additional supports. Problem-solving skills would enable a healthcare worker to identify poor-performing MRDTs and provide alternative (McMorrow et al., 2008).

There is an urgent need for the development of alternative quality control procedure for MRDTs at the facility level. Local microscopy is frequently poorly sensitive and specific, and therefore unsuitable for quality control. One potential solution is development of recombinant protein positive control. A positive control would allow the healthcare worker to test MRDTs on site and frequently monitor MRDT performance, such innovations must be prioritized and thoroughly evaluated in routine implementation sites to ensure that health care workers are able to identify problems with MRDT performance using this tool. Meanwhile, periodic supervision and comparison to reference microscopy may be the best currently available option for quality control at the health facility level (Chanthap et al., 2010).

MRDT performance is measured by testing known dilutions of parasites (typically 200p/µl and 5000p/µl) and a negative control (WHO, 2008). WHO also recommends post-deployment testing at the health facility level, but these recommendations are less developed. Suggested mechanism include sentinel site monitoring, increased training and supervision, and teaching healthcare workers problem-solving skill when RDTs are not performing well. The diagnostic accuracy of RDTs can vary substantially across different geographical areas making it difficult to compare results from studies conducted under non-standard conditions (Wongsrichanalai et al., 2007).

4.2. Ensuring the quality of malaria RDTs

A delayed diagnosis of malaria and the resultant death of a child for whom treatment was withheld owing to a false-negative RDT result will undermine the confidence of both local health workers and the community in RDT-based diagnosis, negating the potential benefits of reduced unnecessary drug use and improved management of non-malarial illness. The introduction of RDTs into a management protocol used to prescribe malaria drugs on the basis of symptoms will result in the withholding of antimalarial treatment from some parasitaemic cases, predominantly those with low parasite density (WHO, 2009). Minimizing this outcome by ensuring high test sensitivity is vital to achieving community acceptance. For health planners to consider adopting RDT use at a local level, and for village health workers and their clients to be confident enough to act on the results, RDTs must provide consistently accurate results, and be seen to do so.

In recent years, the anticipated and actual increases in RDT demand, stimulated by the funding proposals of Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) and other bodies, has resulted in a proliferation of companies manufacturing various RDT devices in North America, Europe, Africa and Asia. However, these small to medium-sized manufacturers have only limited research and development capacity, variable regulatory oversight and certification, and might have a quality assurance (QA) and quality control (QC) policy that is restricted to the bare essentials. Consequently, there is a need to establish procedures to ensure that the QC aspects of malaria RDT manufacture are maintained according to expected performance criteria. Most malaria RDT products come with only scant information on sensitivity, specificity or stability. A review of published field trials will only add to the confusion, as many of the trials of RDTs have demonstrated highly variable and inadequate performance characteristics (Forney et al., 2001; Pattanasin et al., 2003; Richter et al., 2004; Singh et al., 2005). RDTs achieving high sensitivity in some trials perform poorly in others. The only obvious conclusion that can be drawn from these studies is that something is wrong, either with the trial design, the design and QC of many of the commercially available tests, or with both (Mengistu et al., 2003; WHO, 2008).

Unfortunately, inadequate reporting of such trials frequently prevents the likely causes of poor performance from being determined and understood. Standard recommendations on the reporting of diagnostic trials, such as the Standards for Reporting Diagnostic Accuracy (STARD) criteria (Bossuyt et al., 2003; Bell et al., 2006), are not followed in currently published trials, and so are presumably not demanded by most peer-reviewed journals in the field of tropical health. Prospective field trials, are an accepted method of establishing diagnostic accuracy for clinical use, and have a place in guiding procurement and providing evidence for subsequent product improvement.

However, good field trials of malaria RDTs are logistically complicated and costly exercises, and the available malaria RDT product range is wide and rapidly evolving (WHO, 2005; WHO, 2006). Only a limited range of products can be tested in a single trial, with a high likelihood that the results will be redundant owing to product modification by the time of publication of the results. For these reasons, some form of laboratory-based performance test is a necessary prerequisite for screening product suitability for entry into a field trial, to assess variation in performance between tests and batches of a product, and to predict field performance after modification of previously assessed products. Such quality-assured RDTs are required as a precursor for any trial of their operational characteristics, including cost-benefit assessments, disease management behaviour and impact on parasite transmission (Moody, 2002; Chanthap et al., 2010).

4.3. Product testing of MRDTs

To address the need for diagnostic accuracy in procurement, operational use and operational trials, methods for testing the accuracy and stability of malaria RDTs have been developed (WHO, 2003; WHO, 2004; WHO, 2006). A three-tier approach to laboratory-based QC testing is intended to provide the following: first, product testing to demonstrate performance characteristics of antigen detection and specificity, stability and ease of use, characteristics that are essential for making sound procurement decisions; post-purchase lot testing to ensure that the delivered product is consistent with these established performance characteristics; and, a means for the end-user to ensure that the delivered and stored product has retained these qualities. Product-testing and lot-testing allow procurement agencies to make informed decisions on type of MRDTs to purchase, other tools will, in the near future, allow standardized lot-testing at national level and will facilitate standardized testing of the quality of RDTs at clinic level (WHO, 2008).

Development of antigen-based QC samples should be considered in the future, but limited sources of antigens are available at present (Fig 2) and the range of antigens needed to test all RDTs is expected to increase in the near future with the development of new detection systems (WHO, 2006; WHO, 2008).

At present, there is no widely accepted way of assessing the quality of RDTs at the end-user level (Fig. 1); however, the provision of a positive control (sample wells containing the target epitope as lyophilized recombinant antigen) has the potential to provide a level of quality assurance (Lon et al., 2005; Chanthap et al., 2010). The provision of biological samples for developers and manufacturers will facilitate product development and help address the limitations of companies in adequately dealing with internal QA issues. Although a post-purchase QC testing service using cryo-preserved samples is currently available at some laboratories in the WHO network, testing based on lyophilized recombinant antigen in positive-control wells is under development for this purpose, a process that is potentially easier to standardize and sustain (Lon et al., 2005).

Product testing aimed at guiding procurement must also address test sensitivity and specificity, the ease of use for end-users and stability. Stability is not straightforward, as various causes of deterioration in sensitivity, deformation of antigen-binding sites on the signal or capture antibody, de-conjugation of signal antibody, loss of capture antibody from the nitrocellulose paper or changing flow properties along the paper itself, can accumulate over time. These problems are accelerated at higher temperatures, especially if moisture is present through poor or damaged packaging. Decay curves based on the Arrhenius equation, commonly used by manufacturers to estimate shelf life from accelerated stability data, are unlikely to account for the multiple and possibly threshold-dependent mechanisms involved. A combination of accelerated data and real-time data will be necessary to make useful estimations of shelf life. The high temperatures to which RDTs will be exposed to during operational use are unpredictable, and therefore hard to encompass in a field trial alone (Jorgensen et al., 2006).

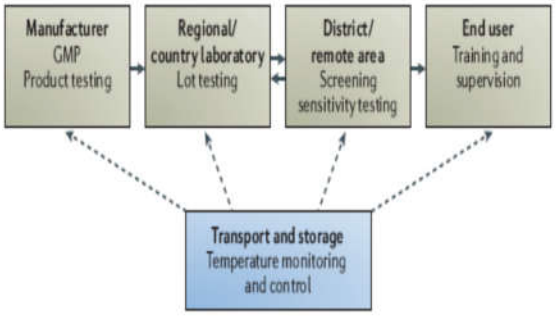

Fig. 1. Outline of requirements for an adequate national quality assurance system for malaria rapid diagnostic test**.**

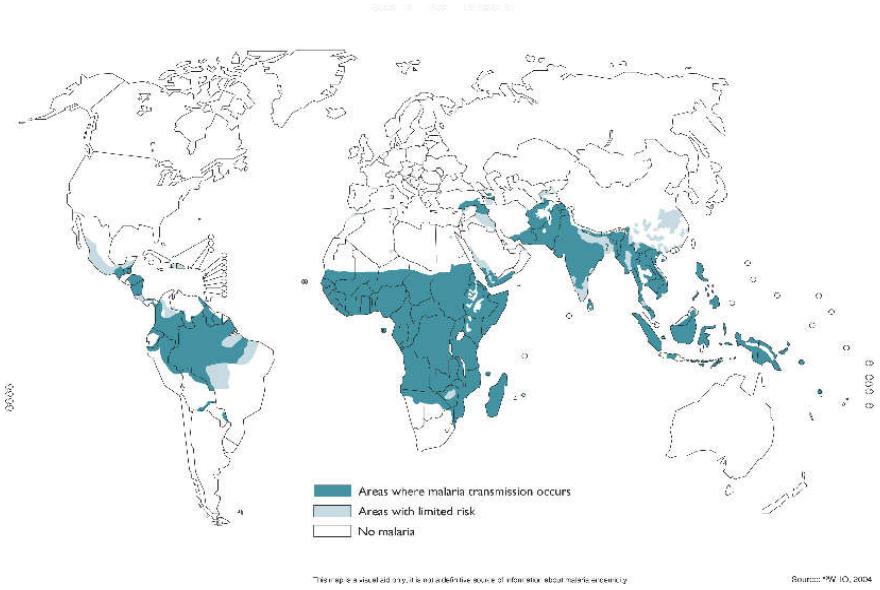

Fig. 2. Collection, testing, Specimen characterization and Global specimen bank for MRDTs lot- testing (Source: WHO- FIND, 2008).

5. Lot testing

Lot-testing of MRDTs involves testing of samples of MRDTs for a manufacturing lot to ensure performance reaches an acceptable standard. This can be done before or after arrival in the country. Lot-testing is important in checking the performance of the RDT; by ensuring that there was no damage of the MRDT during transport to country, to see if there is any lot-lot variation noted in most products, to convince clinicians/users/regulatory authorities that tests are working (WHO, 2008).

World Health Organization (WHO), Tropical Disease and Research (TDR) and Foundation and Innovative for New Diagnostics (FIND) currently support laboratories that perform continual quality assurance of MRDTs in the form of lot testing. This programme responds to requests from national malaria programmes, manufacturers, and procurement bodies to assess the quality of MRDT lots prior to purchase or when they arrive in country, prior to dispersal to the field and clinical use. Testing is performed against parasite-positive and negative panels prepared and characterized in the same way as the panels used in this evaluation. A number of other national institutions have also developed this capacity. Lot-testing reassures MRDTs buyers that the product they have purchased is performing to a high standard before distribution, and helps to ensure that manufacturers produce consistently good lots and improve their products (WHO, 2008).

In the WHO/FIND programme for the evaluation of MRDTs, lots of MRDTs are tested before their use in the field. The programme involves an independent, standardized assessment of MRDTs to guide lot procurement. It is based on an algorithm derived from appropriate testing of lots during procurement and leads to improved MRDTs at points of use. Lots should be tested at purchase because: lots of most products vary; manufacturers are likely to submit unrepresentative, good products for testing; clinicians, users and regulatory authorities must be convinced that the tests work; it is important to ensure that no damage has occurred during transport to a country (post-purchase testing).

The ideal system will be: representative of parasites found in the field; highly standardized, and readily transportable; inexpensive (< 1% of MRDT procurement costs); available to manufacturers to test MRDTs before releasing them; and available to procurement agencies and programmes to test MRDTs before using them (WHO, 2008).

5.1. Panels used for lot-testing

Currently, there are two types of panels. Pre- and post-purchase lot-testing is performed with standardized, diluted wild-type parasites which are subsets of wild types used in the product-testing programme. "Manufacturer panels" are diluted cultured *P. falciparum*, which are subsets of the culture panel used for product-testing, derived from different geographical areas: one Asian, three African and one South American. This panel includes one type C, three type B and one type A HRP-2 structural variants. Its availability is limited, but it is used by some manufacturers (WHO, 2006).

The problems of panel distribution include their limited availability, due to the fact that they are expensive to collect and transport, are difficult to standardize fully and are limited to a few laboratories in order to maintain quality. Wild parasites rather than cultured parasites are used for preparing quality control samples for lot-testing, as the relation between cultured parasite density and antigen concentration in the culture medium is significantly different from that expected *in vivo*.

Parasite quality control samples are derived from fresh blood, prepared and stored in a manner designed to minimize loss of antigen and other changes that may affect MRDT performance. Malaria rapid diagnostic tests are tested against quality control panels diluted at the lowest concentration of 200 parasites and 2000 parasites per microlitre of blood (Fig. 3). This parasite density was chosen instead of 100 parasites per microlitre to prevent incorrect rejection of good-quality tests due to limited microscopy accuracy, inaccurate dilution, loss of antigen during preparation and storage, and the natural variation in the ratio of parasite density to antigen concentration (Gaboa et al., 2010).

5.2. Procedures for lot-testing

Lot testing for *P. falciparum*-only MRDTs, involves initial testing of 22 MRDTs picked from five different MRDTs boxes and long term testing of batteries of eight tests at intervals of 3 months, six times, up to the expiry date. For *P. falciparum* and pan- or *P. vivax* combination MRDTs, lot-testing involves initial testing of 34 MRDTs and repeated testing of 14 tests at intervals of 3 months, six times, up to the expiry date. As spare tests are retained for repeated testing and for sending to confirmation laboratories, 125 RDTs per lot are required for *P. falciparum* only MRDT testing and 175 MRDTs per lot for *P. falciparum* and *P. vivax* combination MRDTs (Fig. 3) (WHO, 2005; WHO, 2008).

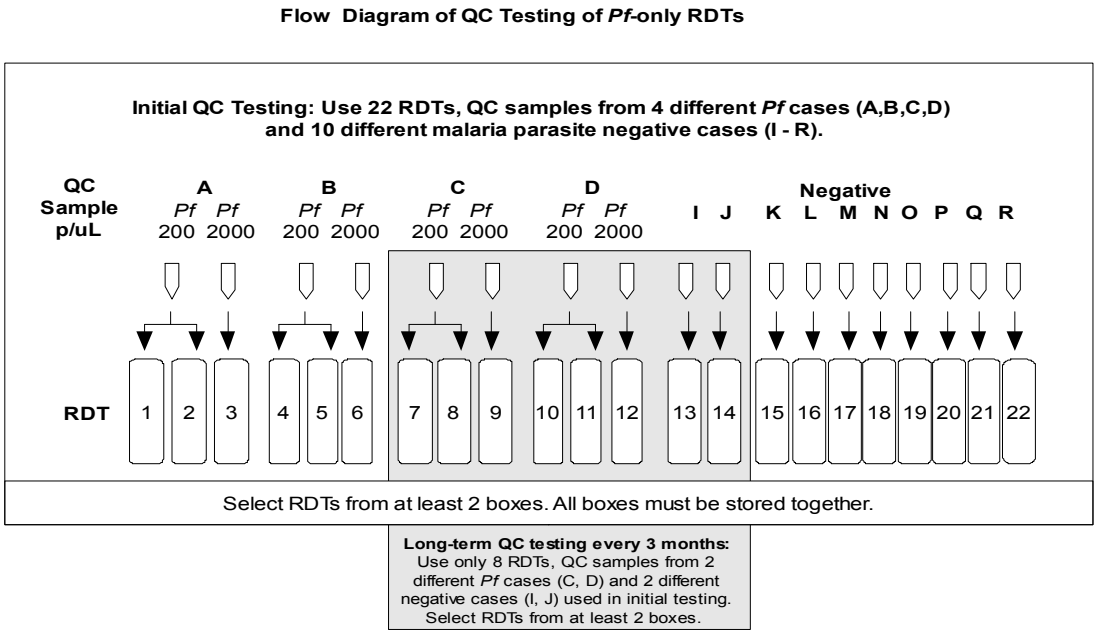

Fig. 3. Flow Diagram of QC Testing of Pf-only MRDTs (Source: WHO-FIND, 2008).

P. falciparum-only MRDTs are tested against four different quality control panels and 10 different negative quality control samples. For each of the four quality control samples, two MRDTs are tested at an aliquot of 200p/ul, and one MRDT is tested at an aliquot of 2000p/ul. One MRDT is tested with each of the 10 negative

quality control samples. *P. falciparum* and pan- or *P. vivax* combination MRDTs are tested against four different *P. falciparum* quality control panels, four *P. vivax* quality control samples and 10 negative quality control samples. For each of the four *P. falciparum* quality control samples, two MRDTs are tested at an aliquot of 200p/µl and one is tested at an aliquot of 2000p/µl. For each of the four *P. vivax* quality control samples, two MRDTs are tested at an aliquot of 200p/µl, and one is tested at an aliquot of 2000p/µ. If the MRDT fails to detect *P. Vivax* at 200p/µl, it is re-tested with a *P. vivax* sample diluted at 500p/µl. One MRDT is performed for each of the 10 negative quality control samples (WHO, 2008).

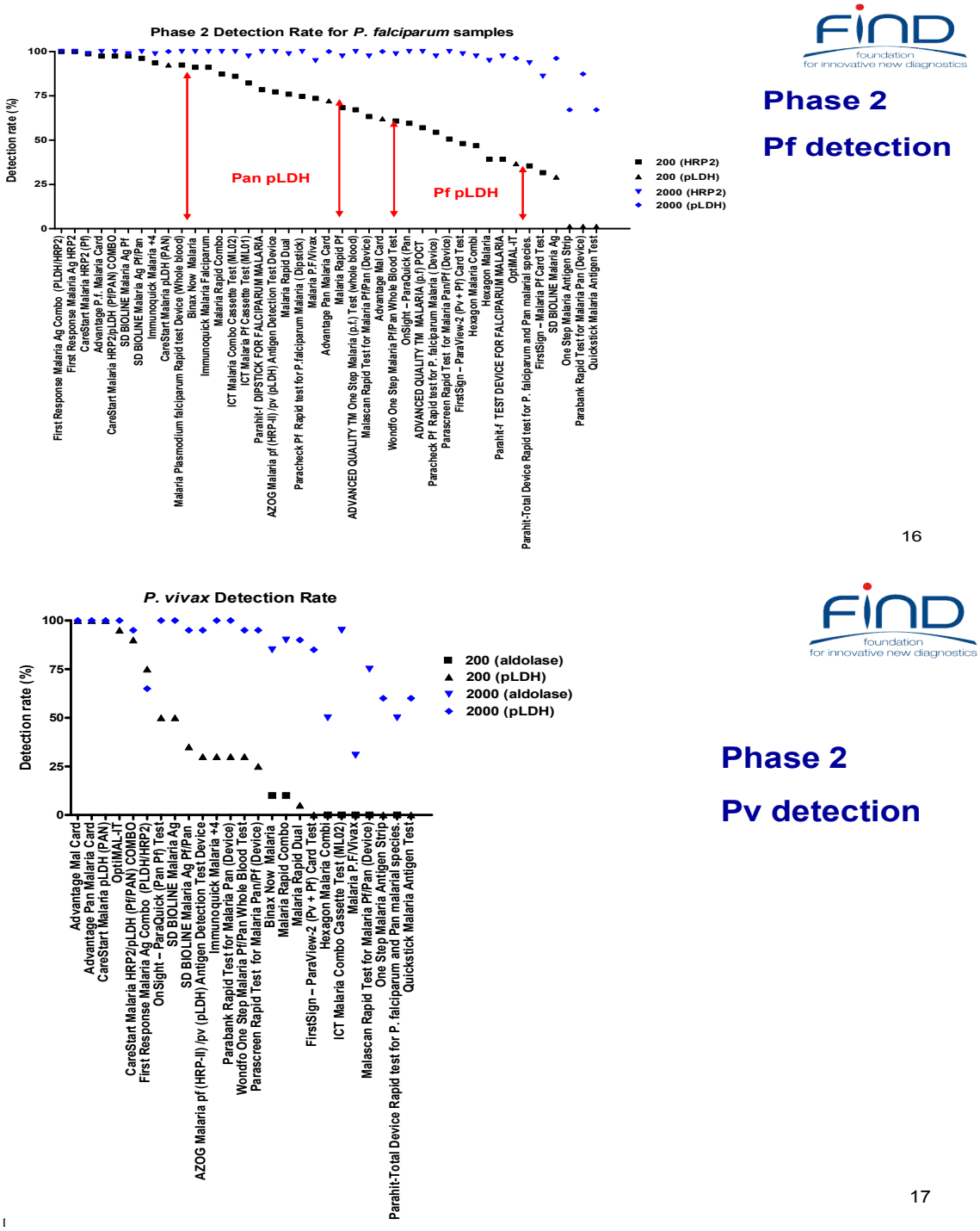

Fig. 4. Phase 2 detection rates for Pv and P.f samples (WHO, 2009).

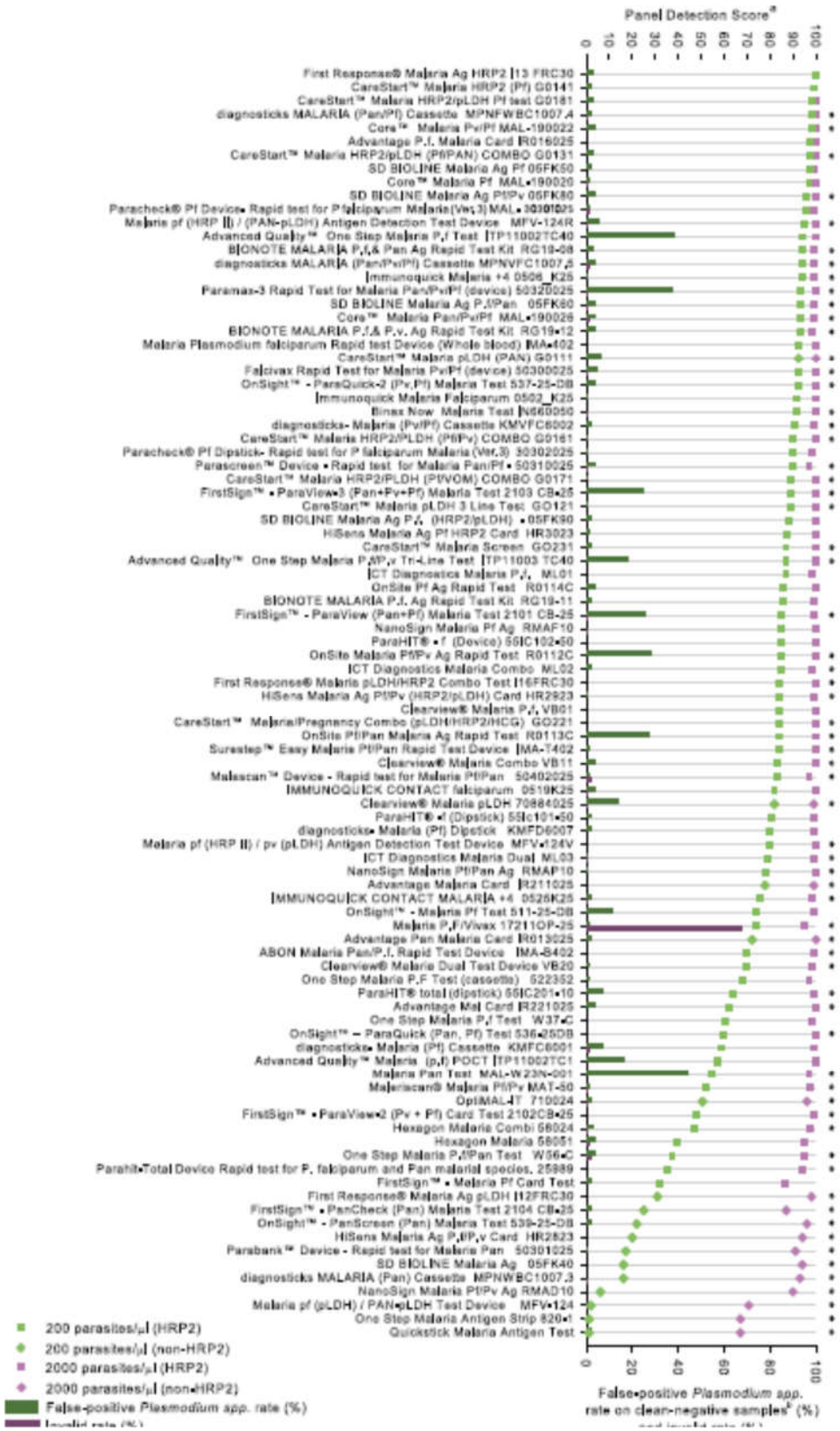

Fig. 5. Malaria RDT Performance in Phase 2 of Rounds 1-3 against wild-type (clinical) samples containing *P.falciparum* at low (200) and high (2000 or 5000) parasites densities (parasites/µl) and clean negative samples.

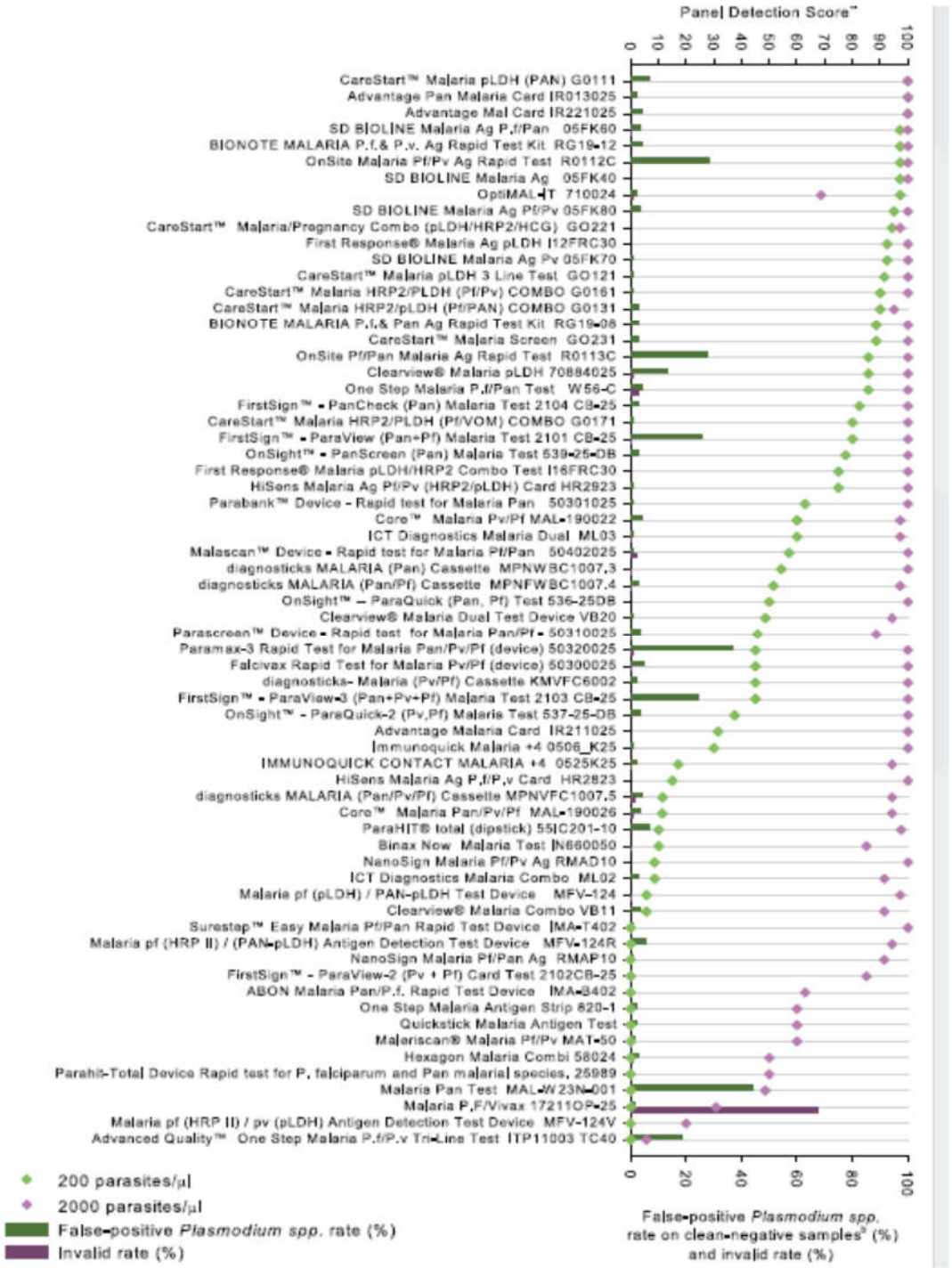

Fig. 6. Malaria RDT Performance in Phase 2 of Rounds 1-3 against wild-type(clinical) samples containing *P.falciparum* at low (200) and high (2000 or 5000) parasites densities (parasites/µl) and clean negative samples.

5.3. Storage of QC samples

Uniformity and reproducibility of QC testing of MRDTs demand stability testing during storage and transport of samples for considerable periods. WHO (2003), indicate that both HRP2 and pLDH are stable in stored blood for up to 6 months at -20^{0}C, HRP2 for considerably longer. Both are stable for at least 2-3 days at 4^{0}C. Repeated freeze-thawing of blood samples will result in premature lysis of red blood cells and parasites and may affect antigen availability and flow characteristics.

Recent use of anti-malarial drugs affects the relationship of parasite density to antigen concentration to varying extent with different antigens (Mayxay et al., 2001; Moody et al., 2000; Eisen et al., 2000). The concentration of pLDH closely mirrors microscopically-patent parasite density. It is, therefore, important that those receiving recent treatment be excluded when parasite donors are selected. This should be determined by careful history taking and a pLDH concentration appropriate for the parasite density (enzyme-linked immuno-sorbent assay (ELISA) will confirm this.

Parasitized and non-parasitized blood for QC samples should therefore be prepared within two days while stored at 4^0C and frozen at -20^{o}C to -70^{o}C. Samples should be transported on dry ice. On thawing, samples should be used within one hour and then discarded. Prior to use, QC samples should be tested to ensure that target antigen concentration is in the correct range. It is noted that the potential for variation in the relative concentration of antigens, and the effects of storage and thawing on blood flow, prevent QC samples developed and stored in this way from being used for direct comparison of the sensitivity of different products. They should only be used for assessment of sufficiency of sensitivity (WHO, 2006).

All QC samples should be screened for the human immunodeficiency viruses (HIV) I and II, Hepatitis B virus (HBV) and Hepatitis C virus (HCV) prior to use. Universal blood safety procedures should be followed during use and disposal.

5.4. Appropriate parasite density

WHO determined that MRDT sensitivity should be close to 100% at 100p/µl (WHO, 2003). It is important to ensure that MRDTs are operating correctly at high parasite densities. Control lines can become faint if insufficient antibody-level conjugate is present when parasite density is high, and test lines may also decline in intensity 'prozone effect' (Forney et al., 2001). Levels for QC testing in laboratories should therefore be set at 100p/µl and at most 5000p/µl.

5.5. Testing the MRDTs

Malaria rapid diagnostic tests lots at release from manufacturers are of uniform quality and MRDTs within the lot will deteriorate at similar rates if kept in uniform conditions. It is therefore necessary to include only a small number for QC testing. Twelve MRDTs from at least two boxes, tested at two different dilutions on four QC samples, and a further MRDT tested on 10 negative samples (Initial testing) (Fig. 3). Laboratory QC testing should occur at least every three months on retained MRDTs until three months before the expiry date. Reports should be sent to the purchaser and manufacturers. The MRDTs should be stored at 2^0C below the maximum storage temperature stated by the manufacturer (Jorgensen et al., 2006; WHO, 2008).

Initial testing should occur prior to release of MRDTs to the field. If MRDTs are tested prior to transport of there remainders of the lot from manufacturer to the purchaser, it is mandatory that temperature be monitored prior to transport of the remainder to the purchaser. Transport to selected MRDTs to the QC facility should occur at 4^0C to ensure no deterioration in quality occurs (WHO, 2008).

5.6. Quality assurance of malaria RDTs after deployment in the field

The degree to which individual/countries malaria control programmes implement MRDT QA schemes will depend on practical and organizational issues. It should be mandatory that large purchases of MRDTs are checked before use and monitored during their shelf-life, practical decisions must be made on the extent of product monitoring at the end user level (WHO, 2009)

Malaria rapid diagnostic test results are compared with microscopy using slides stained on-site and checked centrally with MRDTs which have undergone typical storage and distribution. The MRDTs and blood film should be taken from the same patients in selected health facilities where MRDTs which have undergone typical storage and distribution. Every month, 40 MRDTs (20 positive and 20 negative) should be cross-checked against the corresponding 40 blood film 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 MRDTs should be returned for laboratory testing (Lon et al., 2005)

5.7. Quality assurance on healthcare workers

It is important to perform QA on the health workers performing MRDTs on a regular basis (e.g. every 3 months) in order to: evaluate their capacity of interpreting a set of prepared MRDTs, assessed their technique in

RDT preparation, review diagnosis and treatment records and their ability to ensure good blood safety practices (Tavrow et al., 2000; WHO, 2009).

Appropriate training of healthcare worker is needed prior to introduction on MRDTs, and instructions should be clear, in locally appropriate language and tested. WHO and partners have developed generic job-aids and a training manual for healthcare workers based on trials in Asia and Africa with several partners. These materials are available in English and friendly and can be adapted to other languages (WHO, 2003, Rennie et al., 2007).

5.8. RDT instructions and training (Malaria RDT job-aids and training manuals)

The accuracy of malaria RDTs is dependent on the correctness of preparation and interpretation of the tests. It is essential that users of malaria RDTs have training and instructions in a format and language that they readily understand, and the equipment to carry them out. This helps to ensure the accuracy of the diagnosis, and the safety of the health worker and patient. The generic instructions (job-aids) and training manual are developed with the aim of improving accuracy of RDT diagnosis and blood safety during the diagnostic procedure. The original manual (from which these specific manuals were adapted) was first developed by URC and WHO from materials developed by the Quality Assurance Project (URC), Zambia National Malaria Control Programme (Zambia Ministry of Health) and WHO in Zambia.

The photographic guides to interpretation of malaria RDT cassettes, and questions with model answers, are provided to accompany the generic instructions (job aids) are also available under each section. This manual and the accompanying material are designed to train health workers in the safe and accurate use of malaria rapid diagnostic tests (RDTs).

But correct RDT use is only one part of managing malaria. Health workers also need to know what steps to take after diagnosis, whether the patient is RDT-positive or negative for malaria. National policies for treating malaria differ between countries. Causes of fever also differ. For that reason, this manual addresses only diagnosis, not treatment. Health workers who complete this training on RDT use will also need separate training on your country's national policy for anti-malarial drug use and for appropriate management of RDT-negative febrile cases. RDT designs also differ. If your country is using a different RDT, you may need to modify the training and job aid to fit the brand and type of RDT you are using.

5.9. Positive control wells (PCW)

Development of stable, well-calibrated positive control wells containing recombinant antigens and designed to allow testing of malaria RDTs at the clinic or village levels is a welcomed development in the quality assurance testing of malaria RDTs in the effective case management of malaria. These positive control wells will enable rapid direct evaluation of RDTs performance in remote locations without the need for cross-checking against expert microscopy. Such testing has the potential to increase the confidence of clinicians in the quality of RDTs after transport to remote areas or prolonged storage, allowing them to confidently manage symptoms according to the RDT result.

The specifications for the development of the wells include: good stability in ambient conditions in malaria-endemic areas, low cost (equivalent to an RDT), ease of use, with no additional required chemicals or reagents (reconstitution with clean water), similar viscosity to blood once reconstituted, recombinant proteins of all three common target antigens of *P. falciparum* (HRP2, pLDH, and aldolase), antigen concentration equivalent to a typical parasite sample at 200 p/µl (determined from antigen concentrations of the malaria specimen bank). A panel of wells of containing different target antigens, and variants of 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.

5.10. Use of positive control wells for QA/QC of MRDTs in the field

Malaria rapid diagnostic tests are potential breakthrough in the provision of accurate diagnosis in remote areas, but wide scale use is hampered by uncertainty over accuracy under field conditions. Positive control wells, which contain recombinant malaria parasite antigen, are novel method for address, there is need for QA. The potential of a commercial available positive control well, reconstituted with blood, was assessed for use in routine monitoring of MRDT sensitivity in a remote malaria-endemic region. When maintained at 4^0C, the wells produced a consistent level of pLDH antigen activity, as detected by pLDH - detecting MRDTs, but activity reduced after

cumulative exposure to temperatures likely to be encountered over few months in a malaria-endemic area (Lon et al., 2005)

This limitation was successfully overcome in the field through centralized, controlled storage. Monitoring of MRDT sensitivity was successfully incorporated into routine supervisory visits to remote clinics. However, improved temperature stability of the wells would enhance their potential. The threshold at which the well's signal reduced MRDT sensitivity requires further investigations. The wells show potentials to overcome an important obstacle to the wide implementations of accurate parasite-based diagnosis and appropriate treatment from research data indicate that false-negative results whether due to poor product quality or undetected damage to products after purchase, are likely in widespread operational use of MRDTs (Lon et al., 2005). Together with effects on patient health workers and patients in MRDT use, undermining attempts to introduce parasite-based diagnosis into routine malaria management. This study carried out by Gaye et al. (2004), indicate that positive control wells have the potentials to fill an important gap in monitoring of MRDT quality. While the product and test lacked sufficient temperature stability for prolonged uncontrolled storage in the tropics, it was sufficiently stable to be deployed in remote area (Chiodini et al., 2007).

A positive control well must be stable enough to be stored and used without significant loss of antigen activity. The reconstituted contents must perform similarly to infected human blood at close to the minimum clinically significant parasite density when placed on the RDT, and the wells must be simple and cheap enough to be adopted into routine malaria control programmes (Lon et al., 2005; Gersti et al., 2010).

6. Future directions for quality assurance

6.1. Sustainability and organization within the health service

The initial implementation and maintenance of a QA scheme will involve considerable expense but in long run it will be cost effective. This will include development and distribution of the necessary documentation, laboratory development and training, but may not differ significantly from well-run QA processes for microscopy-based diagnosis. Costs should decrease after establishment, but funding will be needed for laboratory maintenance and supplies, assessment of laboratories, periodic replenishment of QC panels, transport of QC panels, training of end-users and appropriate transport and storage of MRDTs. These processes need more detailed costing. Country budgets for RDTs should routinely include QA costs, but some funding, at least initially, will be required from external sources. Cost-recovery may be possible to some extent for regional-level QC laboratories, both through provision of QC services to countries and through provision of QC panels to manufacturers.

One or two people should be designated to coordinate MRDT QA at a national health service level, coordinating transport, storage, provision of samples for testing, and with oversight of training and monitoring of users. Feedback to other levels of the structure is vital to maintain the commitment and motivation necessary to ensure adequate time and effort is spent.

6.2. Development of new methods for QC testing

It is recommended at present that wild-type parasites form the basis of panels for QC testing. Methods using recombinant antigen should be considered for future development.

These will have the advantage of ease of transport, consistency of quality, and ease of production. At present, there is insufficient information on the relationship of antigen concentration to parasite density, and this may be subject to geographical variation. Curves of antigen concentration versus parasite density should be developed. Costs of development and production may be high, and the introduction of new MRDTs targeting novel antigens would require the development of new QC samples. Antigen-based QC has immediate application in development and use of positive control wells, for use in screening MRDTs in more remote areas to determine the need for more detailed parasite-based laboratory testing (Baker et al., 2005).

6.3. Future priorities for research and RDT development

The escalating use of combination therapies and the increasing importance of demonstration of parasitaemia prior to treatment have increased the need for operational research to guide large-scale implementation of MRDT-based diagnosis. The development of guideline for minimum standards for field trials will improve the ability to compare results of different trials and their value to consumers and manufacturers.

There are several areas in which basic research on MRDT development is still needed, though priorities need reassessment in light of the major foreseeable application of MRDTs in the field. The following recommendations are no longer considered priorities:

- Development of methods that permit quantification of parasite density with MRDTs; Since MRDTs are likely to be used predominantly in remote areas where sophisticated follow-up of patients is not possible, the ability to estimate the total parasite load will be of little clinical importance.
- Development of tests that detect asexual parasitaemia only: It is rare to have gametocytes only in circulation except immediately after treatment. MRDTs detecting pLDH closely reflect viable parasitaemia (Moody et al., 2000; Oduola et al., 1997; Palmer et al., 1999), and are better predictors of treatments failure than HRP-2 detecting MRDTs in the absence of gametocytes (Huong et al., 2002; Wongsrichanalai et al., 1999). However, refinement to distinguish asexual forms from gametocytes will have limited clinical value.

7. Conclusion

Rapid diagnostic test use in malaria diagnosis is rapidly gaining importance and will expand greatly in both volume and area of use over the next few years. The main application in terms of volume of tests is expected to be in remote-area diagnosis in endemic countries. There is a need for further development of MRDTs, particularly in improving sensitivity to non *falciparum species,* in improving stability of tests to maintain adequate sensitivity for *P. falciparum* and in reducing cost. While, WHO should take a role in facilitating such development, present emphasis should be concentrated on ensuring the technology currently available is used to its potential.

Quality assurance process for MRDT is aimed at ensuring high accuracy of tests in the hands of end-users. This will include both monitoring of the technical standard of the MRDTs, processes to minimize environmental insult and training and monitoring of preparation and interpretation by end-users. Quality control describes all the activities taken by a laboratory to monitor each stage of a test procedure to ensure that tests are performed correctly and are accurate and precise. QC must be practical, achievable and affordable. A system for laboratory based assessment for performance of MRDTs throughout their shelf-life and the appropriate standard operating procedures (SOPs).

World Health Organization (WHO), Tropical Disease and Research (TDR) and Foundation and Innovative for New Diagnostics (FIND) currently support laboratories that perform continual quality assurance of MRDTs in the form of lot testing. Lot-testing reassures MRDTs buyers that the product they have purchased is performing to a high standard before distribution, and helps to ensure that manufacturers produce consistently good lots and improve their products (WHO, 2008). Good QA processes for MRDTs will greatly enhance their value to populations at risk and to health systems in endemic countries, providing the evidence necessary to permit greater reliance on MRDT results as a guide to treatment.

Further research and development are needed on quality control testing closer to the point of use of MRDTs, possibly using antigen-containing wells, and on appropriate training and supervision systems for end-users functions. There is also a significant need to improve the quality and flow of information on MRDT testing and use and to develop a good evidence base to guide their introduction into health system. All MRDTs are expected to be stored and transported under the same condition with pharmaceutical products. MRDTs should be stored in a cool environment of not more than 30^{o}C. The provision of a "cool chain" for shipment and storage of MRDTs is essential within the health facilities. In view of our prevailing temperature which could be above 30ºC to 40ºC during the day, transportation of MRDTs by road should be carried out in a covered vehicle with attention to ambient temperature while the vehicles are moving and if parked. Avoid leaving MRDTs in vehicles parked in the sun.

Quality assurance process for MRDTs is the provision of PCW, composed of recombinant antigen at concentrations intended to give a weak-positive results that should allow the village health worker or care provider to test an MRDTs from any box before use, ensuring that the kit has not degraded during storage and transport, and boostering confidence that the results of testing may be used to direct therapy. This development promises to greatly improve on the current need to perform comparative microscopy at sentinel sites to monitor MRDT field performance and this would the boost the current policy on parasite base confirmation and assist in malaria case management (Perkins and Bells, 2008; Gersti et al., 2010).

Recommendation

Sensitivity of MRDTs must be checked at a central laboratory on receipt from the manufacturer, and periodically the recommended shield life at a temperature during storage at a temperature close to the maximum recommended by the manufacturer. Instructions for MRDT preparation and interpretation should be clear and concise in local languages. Health workers using the tests should be trained and assessed, and systematically monitored on test preparation and interpretation (Nicastri et al., 2009).

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