1. EXECUTIVE SUMMARY

1.1. INTRODUCTION

The World Health Organization estimates that 3.3 billion persons were at risk of acquiring malaria in 2006, with 247 million of these developing clinical malaria (86% in Africa), and nearly 1 million (mostly African children) dying from the disease. Malaria remains endemic in 109 countries, and while parasite-based diagnosis is increasing, most suspected cases of malaria are still not properly identified, with accurate diagnosis and disease monitoring consequently remaining elusive (*1*).

WHO recommends that malaria case management be based on parasite-based diagnosis in all cases, with the exception of young children in areas of high transmission and where lack of resources or need for urgent response temporarily limits its application. The use of antigen-detecting rapid diagnostic tests (RDTs) forms a vital part of this strategy, providing the possibility of parasite-based diagnosis in areas where good quality microscopy can not be maintained. The number of RDTs available, and the scale of their use, has rapidly increased over the past few years. However, limitations of comparative field trials and the heterogeneous nature of malaria transmission has limited the availability of good quality performance data that national malaria programmes require to make informed decisions on procurement and implementation. To this end in 2006, WHO and FIND (Foundation for Innovative New Diagnostics) launched an evaluation program to assess the performance of commercially available malaria RDTs and allow direct product comparisons that would assist WHO, other UN agencies and national governments in making procurement decisions and would ultimately encourage improvement in the quality of manufacturing.

1.2. THE WHO PRODUCT TESTING PROGRAMME

This report, which presents the results of the first round of WHO product testing of malaria antigen-detecting RDTs, was completed in November 2008 in collaboration with FIND, the US Centers for Disease Control and Prevention (CDC) and other partners (Fig.2). All companies manufacturing under ISO-13485 Quality System Standard were invited to submit up to 3 tests for evaluation under the programme. In this first round of testing, 41 products from 21 manufacturers were evaluated against prepared blood panels of cultured *Plasmodium falciparum* parasites and patient-derived *P. falciparum* and *P. vivax* parasites, and a parasite-negative panel. Thermal stability was assessed after 2 months of storage at elevated temperature and humidity, and a descriptive ease of use assessment was recorded. Of the 41 products, 16 detect *P. falciparum* alone, 22 detect and differentiate *P. falciparum* from non-*P. falciparum* malaria[1], and 3 detect *P. falciparum* and non-*P. falciparum* malaria without distinguishing between them. Manufacturers submitted 2 lots of each product for evaluation.

The evaluation is designed to provide comparative data on the performance of the submitted production lots of each product. Such data will be used to guide procurement decisions of WHO and other UN agencies and national governments. Product testing is part of a continuing programme of work to improve the quality of RDTs that are used, and to support broad implementation of reliable malaria diagnosis in areas where malaria is prevalent. A second round of product testing began in April 2009. It is anticipated that a further round will be undertaken in 2010, with a call for expressions of interest later in 2009.

1.3. RESULTS OF THE EVALUATION

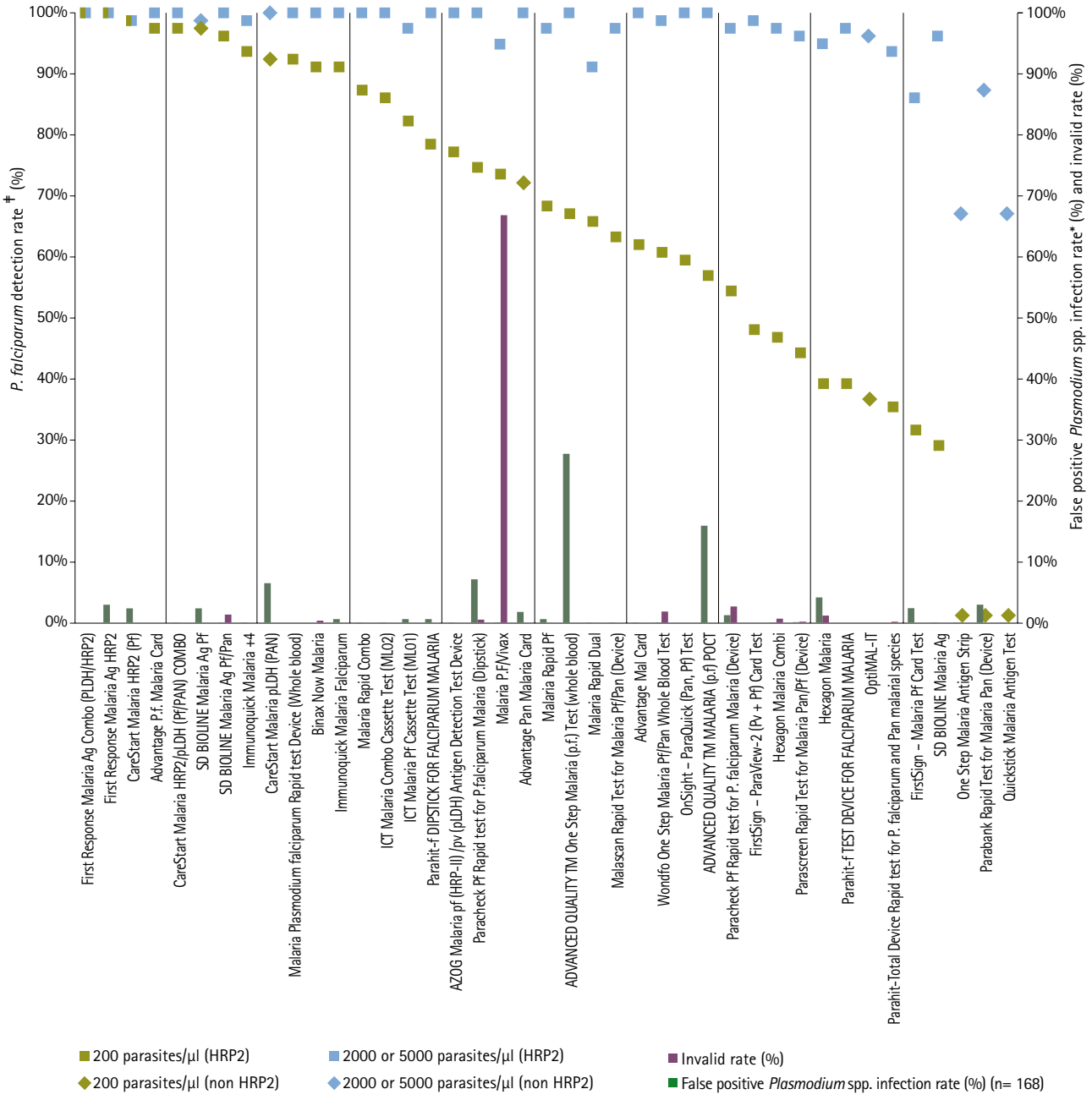
The results (summarized in Tables 3, 3a, 4, 4a and Figure E1) provide comparative data on 2 lots of products against a panel of parasite samples diluted to a low parasite density (200 parasites/µL) and a higher parasite density (2000 or 5000 parasites/µL). The former is below the mean parasite density found in many populations with endemic malaria. For the purposes of this report, 'detection rate' of a product is the percentage of malaria samples in the panel giving a positive result by two RDTs per lot at the lower parasite density, and a single RDT per lot at the higher parasite density. Thus, it is not a measure of RDT clinical sensitivity, or positivity rate against the panel but rather a combined measure of positivity rate, along with inter-test and inter-lot consistency.

The clinical sensitivity of an RDT to detect malaria is highly dependent on the local conditions, including parasite density, in the target population, and so will vary highly between malaria-endemic populations. The results in this report show comparative performance between RDTs, and give an idea of which products are likely to provide higher sensitivity in the field, particularly in populations with low-density infections. As the detection rate at 2000 parasites/µL indicates, the sensitivity of many of these products will be similar in populations with higher parasite densities, although a subset of any population will include vulnerable individuals who may develop illness at low parasite densities (e.g. young children, pregnant women, those well protected by bed nets) and must always be taken into account when interpreting RDT results.

Heat stability (summarized in Table 5) is vital to maintaining sensitivity of the test in the field. As a result, for procurement, it is essential that careful consideration be given to stability results to ensure that products to be used in areas with high temperatures of transport and storage have demonstrated great stability in the product testing programme. Requirements will vary between countries: for example, if tests are to be deployed in areas where temperatures rarely rise above 30°C, less emphasis needs to be placed on stability at high temperatures.

1 One is *P. vivax* specific

Figure E1: Summary performance of malaria RDTs against blood samples containing wild type *P. falciparum* at low (200) and high (2000 or 5000) parasite densities (parasites/µl) and malaria-negative samples.



Pf - *Plasmodium falciparum*
Pv - *Plasmodium vivax*
pan - Plasmodium species

ǂ - A sample is considered detected only if all RDTs from both lots read by the first technician, at minimum specified reading time, are positive. Phase 2 Evaluation Panel: 79 *P. falciparum* wild type samples; 20 *P. vivax* wild type samples and 90 *Plasmodium* spp. negative samples. Rapid diagnostic tests (RDTs) - 2 tests x 2 lots at 200 parasites/µl and 1 test x 2 lots at 2000 parasites/µl

* - The total number of times a positive result for malaria was generated when it should not have been (Pf+; Pf +/Pan or Pv -; Pf+/Pan or Pv+; Pf-/Pan or Pv+)

Ease of use requirements will also vary, depending on the extent of training and the work environment of the end-users. Particularly in primary health care settings, the simpler the tests, the easier it will be to avoid errors in preparation and interpretation.

1.4. SUMMARY OF OUTCOMES

- There is now a mechanism in place that allows laboratory-based evaluation of RDT performance in a standardized way to distinguish between well and poorly performing tests to inform procurement and prioritization for entry into WHO prequalification and procurement schemes.
- Several RDTs are available that demonstrated consistent detection of malaria at low parasite densities (200 parasites/µl), have low false positive rates, are stable at tropical temperatures, are relatively easy to use, and can detect *P. falciparum*, *P. vivax* infections, or both.
- Performance between products varied widely at low parasite density (200 parasites/µl); however, most products showed a high level of detection at 2000 or 5000 parasites/µl.
- *P. falciparum* tests targeting HRP2 antigen demonstrated the highest detection rates, but some tests targeting pLDH also exhibited high detection rates.
- Test performance varied between lots, and widely between similar products, confirming the advisability of lot-testing post purchase and prior to use in the field.
- The results underscore the need for manufacturers to have adequate reference materials for product development and lot-release. The WHO-FIND malaria RDT evaluation programme, in collaboration with the CDC, will soon offer quality standard panels to manufacturers to assist in this process.

1.5. USE OF THESE RESULTS

Ultimately, it is imperative that procurement decisions based on these results take into consideration local conditions of malaria transmission and illness where the tests will be used (e.g. *Plasmodium* species, target antigen variation, parasite densities, climate). Procurement of RDTs must not occur without programmatic and infrastructure preparation for proper use, including supply chain management, training on test usage and disposal, and training on patient management in response to results. This report provides an algorithm to assist in this decision-making process (Annex 5).