Malaria Rapid Diagnostic Test Performance

Summary results of WHO product testing of malaria RDTs: Round 1-5 (2008-2013)

World Health Organization

FIND
foundation for innovative new diagnostics

CDC

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WHO Library Cataloguing-in-Publication Data:

Malaria Rapid Diagnostic Test Performance: Summary results of WHO product testing of malaria RDTs: Round 1-5 (2008-2013)

1.Diagnostic Techniques and Procedures. 2.Malaria - diagnosis. 3.Diagnostic Tests, Routine - methods. I.World Health Organization.

ISBN 978 92 4 150763 9 (NLM classification: WC 750)

Layout: Bruno Duret - Editor: Elisabeth Heseltine

Printed in Italy

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The WHO Programme of Prequalification of Diagnostics and Medical Devices uses the results of the WHO Malaria RDT Product Testing Programme as the laboratory evaluation component of the prequalification process for malaria RDTs. Although not currently a requirement for WHO procurement, manufacturers are encouraged to apply for WHO prequalification. A regularly updated list of WHO-prequalified diagnostics, including malaria RDTs, is available at *http://www.who.int/diagnostics_laboratory/evaluations/PQ_list/en/*.

WHO recommendations for procurement of malaria RDTs are currently based on the attainment of a set of minimum performance criteria in the WHO Malaria RDT Product Testing Programme. These recommendations were established by the WHO Malaria Policy Advisory Committee in 2012 , are outlined in this report and presented in full in a WHO information note (available at *http://www.who.int/malaria/publications/atoz/rdt_selection_criteria_en.pdf?ua=1*).Products that do not meet the full set of minimum performance criteria are not eligible for procurement by WHO.

The lists of RDTs included in this report are not exhaustive lists of malaria RDTs. These lists reflect those products which have been submitted for evaluation in Rounds 2-5 of the WHO Malaria RDT Product Testing Programme, and indicate to what extent these products, as manufactured by the listed companies, were -at the time of their evaluation- found to meet the above mentioned set of minimum performance criteria. The evaluation results indicated in the figures and tables apply only to the specific product as listed with its unique product code / catalogue number and as manufactured by the listed company.

The improper storage, transport and handling of malaria RDTs may affect their level of performance.

The fact that certain products are not included in the lists and figures in this report indicates that they have not or not yet been submitted for evaluation in the WHO Malaria RDT Product Testing Programme, or that their evaluation has not yet been completed and published in [a new edition of this report]. It does not however indicate anything in respect of such products' performance. The lists and figures are updated regularly, and malaria RDTs are added to the lists and figures as and when (following the voluntary participation in the WHO Malaria RDT Product Testing Programme) their evaluation against the above mentioned set of minimum performance criteria has been completed.

Although the malaria RDTs listed in the tables and figures are regularly re-evaluated, and updated evaluation results are published by WHO, WHO cannot represent that products included in the lists and figures will continue to meet the performance criteria in the same manner as indicated. WHO recommends therefore that before procurement of a malaria RDT, each lot of that product undergoes lot testing at one of the two following lot-testing laboratories: Institut Pasteur du Cambodge (IPC), Cambodia or Research Institute for Tropical Medicine (RITM), The Philippines.

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This report may not be used by manufacturers and suppliers for commercial or promotional purposes.

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1. SUMMARY OF PERFORMANCE OF RAPID DIAGNOSTIC TESTS FOR MALARIA: WHO PRODUCT TESTING ROUNDS 1–5

1.1. Introduction

WHO estimates that half the world's population is at risk of malaria. In 2012, there were an estimated 207 million cases (with an uncertainty range of 135 million to 287 million) and an estimated 627 000 deaths (with an uncertainty range of 473 000 to 789 000). Approximately 90% of all malaria deaths occur in sub-Saharan Africa, and 77% occur in children under 5 years. Malaria remains endemic in 104 countries, and, while parasite-based diagnosis is increasing, most suspected cases of malaria are still not properly confirmed, resulting in over-use of antimalarial drugs and poor disease monitoring (*1*).

WHO recommends that malaria case management be based on parasite diagnosis in all cases (*2*). The use of antigen-detecting rapid diagnostic tests (RDTs) is a vital part of this strategy, forming the basis for extending access to malaria diagnosis by providing parasite-based diagnosis in areas where good-quality microscopy cannot be maintained. The number of RDTs available and the scale of their use have increased rapidly over the past few years; however, limitations of field trials and the heterogeneous nature of malaria transmission have limited the availability of the good-quality data on performance that national malaria programmes require to make informed decisions on procurement and implementation, and it is difficult to extrapolate the results of field trials to different populations and times. Therefore, in 2006, the WHO Special Programme for Research and Training in Tropical Diseases (TDR) and the Foundation for Innovative New Diagnostics (FIND) launched a programme to systematically evaluate and compare the performance of commercially available malaria RDTs. The results of WHO's malaria RDT product testing have been published annually since 2009 and form the basis of the procurement criteria of WHO, other United Nations agencies, the Global Fund to Fight AIDS, Tuberculosis and Malaria, national governments and nongovernmental organizations. The data have guided procurement decisions, which, in turn, have shifted markets towards better-performing tests[1] and are driving overall improvements in the quality of manufacturing.

This summary presents an overview of the results of rounds 1–5 of malaria RDT product testing and key concepts for understanding and using the results. It is published in conjunction with the release of the full report on round 5. The results of all rounds of testing should be considered as a single data set. The separate, full reports of each round (*3–6*) should be consulted for further details of methods, product performance and interpretation of the results.

1.2. The WHO product testing programme

The RDT evaluations summarized here were performed in collaboration by WHO, TDR, FIND, the United States Centers for Disease Control and Prevention (CDC) and other partners.[1] All companies that manufacture according to the ISO 13485:2003 quality system standard were invited to submit one to three products for evaluation in the programme. In each round of testing, products are evaluated against geographically diverse, cryopreserved *Plasmodium falciparum* and *P. vivax* clinical samples diluted to 200 and 2000 parasites/μL and with consistently comparable concentration ranges of histidine-rich protein II (HRP2), *Plasmodium* lactate dehydrogenase (pLDH) and aldolase determined by quantitative enzyme-linked immunosorbent assay (ELISA) (Annex S1). In the first round of testing, 41 products from 21 manufacturers were evaluated against prepared blood panels of cultured *P. falciparum* parasites, while 29, 50, 48 and 42 products from 13, 23, 27 and 34 manufacturers were evaluated in rounds 2, 3, 4 and 5, respectively. Of these 210 products, 206 progressed to testing against panels of 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 assessment of ease of use was made. Many manufacturers have decided voluntarily to submit products to one or more rounds of testing, and, in round 5, a requirement was instituted to resubmit products for re-evaluation within 5 years of original testing (Table S1). Of the 206 fully evaluated products, 32 have been evaluated twice, 11 have been evaluated three times and two evaluated four times in rounds 1–5. Of the 147 unique products tested in the programme, 36 detect *P. falciparum* alone, 101 detect and differentiate *P. falciparum* from non-*P. falciparum* malaria (either pan-specific or species-specific for *P. vivax* or *P. vivax*, *ovale* and *malariae*), 9 detect *P. falciparum* and non-*P. falciparum* malaria without distinguishing between them, and one product was designed to detect *P. vivax* only. Manufacturers submitted two lots of each product for evaluation. When the same products (*7*) were resubmitted in subsequent rounds of testing, the second set of results replaced those from the earlier round. Thus, the performance of some tests in the results below differs from that reported in rounds 1–4.

Of the 22 products due for compulsory retesting in round 5, 10 were submitted (Table S1). Round 1 products that were not

[1] See full reports of rounds 1–5 (3–6) for lists of collaborating partners.

resubmitted have been removed from the figures and tables in this summary performance document.

The aim of the evaluation is to provide comparative data on the performance of the submitted production lots of each product. These data will be used to guide procurement decisions by WHO, other United Nations agencies and national governments and constitute the laboratory evaluation component of the WHO prequalification process for malaria RDTs (*8*). Product testing is part of a continuing programme of work to improve the quality of RDTs in use and to ensure reliable malaria diagnosis in areas where malaria is prevalent. A sixth round of product testing will begin in June 2014.

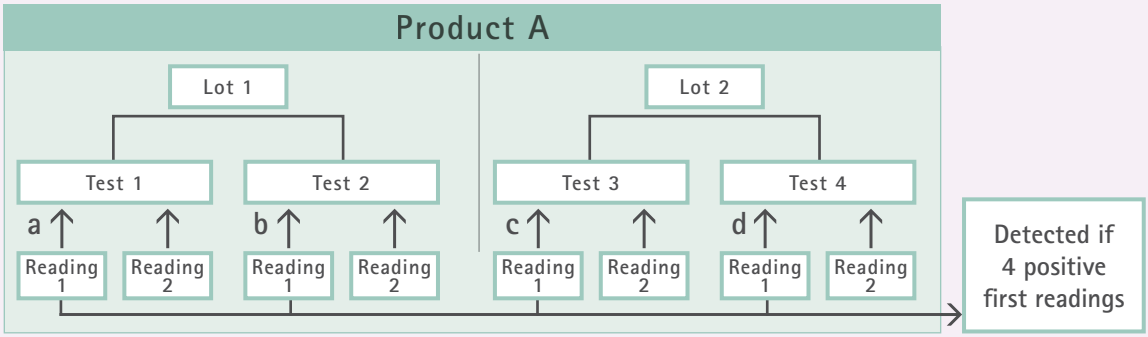
1.3. Panel detection score and other results of the evaluation

The results (summarized in Figs S1–S3 and Tables S2 and S3) provide comparative data on two 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 well below the mean parasite density found in many populations with endemic malaria and is considered close to the threshold that must be detected in order reliably to identify clinical malaria in many settings (*9*). For the purposes of this report, the main measure of performance is the panel detection score (PDS);[1] for each RDT evaluated, the PDS is measured separately at the

[1] Termed "detection rate" in the full report of round 1, published in 2009.

Box 1: Example calculation of panel detection score and positivity rate for product A against a sample density of 200 parasites/µL

The first reading was at the minimum time specified by the manufacturer; the second reading was up to 30 min later[a]. A sample is considered detected only if all first test readings, from both lots, are positive, i.e. readings a, b, c and d must be positive.



[a] second reading results are for internal use only

P. falciparum sample	a	b	c	d