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Letter to the Editor

Malaria Rapid Diagnostic Tests: One Size May Not Fit All

Anthony Moody (5) provides a comprehensive and balanced review of the expanding range of malaria rapid diagnostic tests (RDTs). However, in discussing the utility and disadvantages of RDTs, Moody and others (8) do not clearly distinguish between the different contexts in which they may be used, leaving the impression that a "one size fits all" test is needed. Some of the claimed limitations of present RDTs are not necessarily a disadvantage when compared to current microscopy-based diagnosis.

In common with most studies of RDTs, Moody emphasizes the place of microscopy as a "gold standard," albeit noting that this standard is flawed and can be expected to detect only ≥100 parasites/μl in nonspecialized laboratories. Sensitivity is further reduced when slide staining is delayed (4). Even expert microscopy is incapable of detecting many parasitemic individuals in areas of endemicity where chronic *Plasmodium falciparum* infections with low, fluctuating parasite density and transient, mild symptoms are expected (3, 6). As Moody suggests, detection and treatment of such cases may not be of great clinical significance, but these cases will commonly be gametocytemic (3) and therefore perpetuate transmission. Detection of persisting antigens such as histidine-rich protein II (HRPII) may therefore offer an advantage, as transient peaks in parasite density likely to be missed by microscopy will leave a trail of circulating antigens, widening the temporal window over which peaks in parasite density can be detected by RDTs. This would explain the high frequencies of "false positive" HRPII detection recorded in remote areas (2, 7), where gold standard microscopy based on a single blood sample cannot be expected to be accurate. Moody rightly states that "a negative RDT cannot at present be accepted at face value and will need to be confirmed by microscopic examination," but this statement could as easily be reversed.

Persistence of circulating antigen is also considered a disadvantage by Moody and others (8), as it precludes short-term treatment monitoring. This is of limited relevance to many areas of endemicity, as available resources and remoteness do not allow microscopy-based treatment monitoring at present. This limitation of RDTs would be of practical significance in such areas only if a dramatic reduction in price allows multiple tests per patient. Where clinical resistance is suspected, microscopy could still be used.

Due to difficulties in providing skilled, readily available microscopy, there is no real alternative to RDTs at present in many areas of endemicity if a blood-based diagnosis is to be made; symptom-based diagnosis must miss many infectious cases if gross overtreatment is to be avoided (1, 2). It is important to ensure that further development and deployment of RDTs is not driven solely by the needs of resource-rich customers such as the military and travel markets, aiming primarily at early detection of severe acute malaria, while neglecting the immediate need for a more accurate method of detecting and interrupting transmission in resource-poor areas. Perhaps we should be looking more closely at what needs to be achieved with RDTs and consider a range of formats tailored for specific situations.

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Author's Reply

I am grateful to David Bell for extending the discussion on the role of RDT for malaria diagnosis. As with most nonsubjective tests, the application of any new technology must be examined to find its place in clinical diagnosis in any given area.

The areas where malaria is nonendemic do require a test system that will detect any parasitemia present, and as the majority of the population in these areas are nonimmune, the question of the subpatent infections is usually not encountered. In these circumstances the most sensitive method available for malaria detection is still microscopy, and RDTs are slowly finding a role in the laboratory when expert microscopy is not available. Short-term posttreatment monitoring with RDTs can be of significant value. Persisting antigen detection with HRPII may confuse treatment monitoring but can be useful when unknown therapy for a clinical diagnosis for malaria has been given prior to returning home.

I agree with David Bell that areas where malaria is endemic present a greater challenge for the RDT. Subpatent and fluctuating parasitemia are present and may present a diagnostic challenge but are frequently asymptomatic and are necessary for retaining the antigenic stimuli for protective immunity. The

current sensitivity of RDTs for primary diagnosis may not be adequate to reflect all levels of parasitemia present but should not "overdiagnose" parasitemias from asymptomatic cases. This is a very sensitive balance, and because most acute malaria in areas of endemicity occurs among children, the use of RDTs in these circumstances may not be sufficiently sensitive to replace microscopy at present. Detecting persistent antigenemia by using HRPII-based RDTs does have a role in epidemiological awareness, but at present they are not capable of differentiating between a continuing asexual parasitemia and gametocytemia.

The current format of available RDTs presents two possible diagnostic tools. RDTs that detect parasite enzymes are sensitive diagnostic tools that can also be used to monitor a declining parasitemia with viable parasites; this may not be economically feasible in all circumstances but is technically available and clinically useful. Parasite enzymes tend not to be present beyond clearance of peripheral blood parasites and parallel most closely the microscopic findings.

Tests based on detection of *P. falciparum* HRPII antigen are also sensitive tools, but antigenemia can persist beyond clearance of asexual parasitemia. Persistence of HRPII can be found with residual gametocytes, which may present a public health risk for continued malaria transmission in areas of endemicity but may present a conundrum to physicians in case of failed therapy. In some areas where malaria is endemic, attempts are made to try to eliminate the gametocyte risk by treating patients with an appropriate secondary drug. I know of no study that has been made to evaluate the detection of gametocytes alone using RDTs, and perhaps this issue needs to be examined.

I am aware that the next generation of enzyme-based RDTs will offer a more useful malaria speciation option. I agree that the questions of improving sensitivity and examining the presence of persistent gametocytemia detection, along with costing stability, should be foremost in the malaria RDT development program for diagnostic products. The difficult question of "approval for use" in certain countries is also being addressed by manufacturers in Europe, but Food and Drug Administration approval has not yet been given to these products.

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