EDITORIAL COMMENTARY

Risks and Benefits of Targeted Malaria Treatment Based on Rapid Diagnostic Test Results

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(See the article by d'Acremont et al, on pages 506–511.)

In this issue of *Clinical Infectious Diseases*, d'Acremont et al [1] importantly address the clinical safety of withholding antimalarial treatment in febrile children who have a negative result for one of the newly developed rapid diagnostic tests (RDTs) for malaria.

Restricting malaria treatment to patients with parasitologically confirmed malaria infection has become increasingly important in the era of artemisinin-based combination therapy (ACT). This importance is reflected in the World Health Organization's new recommendation: "Prompt parasitological confirmation by microscopy or alternatively by RDTs is recommended in all patients suspected of malaria before treatment is started. Treatment solely on the basis of clinical suspicion should only be considered when a parasitological diagnosis is not accessible" [2, p 13]. The rationale for this is that unnecessary antimalarial treatment will put non–malaria-infected patients at risk of adverse drug events and, importantly, also will increase the exposure of low residual concentrations of the slowly eliminated partner drugs in ACT to infecting parasites, with potential selection of drug tolerance and resistance [3, 4]. Moreover, unnecessary presumptive ACT treatment is costly and may prevent other causes of fever from being considered, being identified, and being appropriately treated. Thus, improved and well-targeted antimalarial treatment may result in overall better health outcome, which in turn could support the credibility of recommended treatment policies (eg, the recently introduced ACTs). These aspects apply especially in areas with low prevalence of malaria.

There is ongoing debate as to which diagnostic method (mainly light microscopy or RDT) may be most effective in primary health care facilities in Sub-Saharan Africa. However, in settings with limited resources, RDTs may be the best option [5]. Although there may be significant variations between different devices and even between different lots, RDTs for *Plasmodium falciparum* malaria are often both sensitive and specific [6]. Hence, RDTs have been proposed for primary health care settings within public and private sectors and even potentially for community-based health care ("home management"), in the hands of community-based health care workers.

It is important to highlight another aspect of restricted ACT prescription (ie, ACT prescription dependent on malaria diagnosis). Any diagnostic test is associated with the risk of a missed malaria diagnosis (ie, a false-negative test result) and thus a remaining untreated malaria infection [7]. Of special concern in this regard are patients with no or little malaria immunity (eg, small children in Sub-Saharan Africa), for whom the risk of developing severe malaria may be high. Fear of leaving such children without necessary antimalarial treatment because of a false-negative RDT result is quoted as a key reason for possibly poor adherence to test result protocol in real-life situations. Previous studies conducted in Africa found that >50% of children with fever who had a negative RDT result were being prescribed antimalarial drugs as their main treatment [8–10]. However, 2 other studies have in contrast provided evidence of high adherence to protocol for negative RDT results, 1 from the Tanzania mainland [11] and 1 from Zanzibar [12], by withholding antimalarial treatment.

The risk of a false-negative RDT result depends on several factors: the RDT itself (brand and even lot variation, including performance in practice) and malaria species, density, and background prevalence. Well-performed laboratory studies have shown RDT sensitivities to be generally

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>95% for *P. falciparum* densities of 1000–2000 parasites/μL, whereas the corresponding rates for densities of 100–1000 parasites/μL have been lower, but mostly >75%. Under field conditions (ie, primary health care), sensitivities have been generally >90% but again have been dependent on parasite density [13]. Hence, in 1 large recent study, the sensitivity of a common histidine-rich protein 2–based *P. falciparum* test was >99% for a density of $\geqslant$1000 parasites/μL but only 76% for a density of 100–999 parasites/μL [12].

The potential risk of withholding antimalarial drugs in febrile children with negative RDT results in Tanzania was studied by d'Acremont et al [1] in 2 health centers, 1 urban and 1 rural. Of the 987 children with fever who were enrolled in the 2 study sites and who were followed up, 396 children with positive RDT results were treated for malaria, whereas 591 with negative RDT results were not. The number of malaria patients who were missed because of false-negative RDT results and consequently were nontreated cannot be estimated in this study, because no concomitant blood smear microscopy or molecular diagnostic technique was included at day of enrollment. D'Acremont et al used ParaHit-f, a histidine-rich protein 2–based test for *P. falciparum,* in their trial. Sensitivities of such tests may be in the order of 90%–95% for parasite densities >100 μL [6, 12, 13]. This suggests that an estimated 20–40 *P. falciparum* infections may have been missed in the present study, a majority probably being low-density parasitemias at enrollment. Interestingly, a total of only 5 patients with remaining and/or recurrent symptoms were found to be malaria-positive during the 7-day follow-up period, this time by microscopical examination. Development of severe disease manifestations of *P. falciparum* malaria in most cases of uncomplicated malaria would be expected to occur within 7 days in children who have been left untreated. However, in patients with fever, possibly due to other causes but with concomitant low *P. falciparum* densities, periods >7 days may be required before malaria-associated clinical symptoms and even severe manifestations, such as severe anemia, develop [14]. Another critical aspect in the study of d'Acremont et al [1] is that almost all (94%) of the children with negative RDT results were treated with antibiotics, including cotrimoxazole, an antibiotic with known antimalarial effect. Such treatment may have suppressed some low-density *P. falciparum* infections, potentially resulting in an underestimation of the risk of developing clinical malaria during the 7-day follow-up. Therefore, it cannot be ruled out that a follow-up >7 days and a more restricted use and choice of antibiotics would have identified additional malaria infections among children with negative RDT results.

The findings by d'Acremont et al [1] are comparable with previous findings from Zanzibar [12], although that study included patients of all age groups. In the Zanzibar study [12], only 5 of 26 patients with fever whose RDT result was retrospectively confirmed by microscopy to be a false-negative were parasite-positive when retested <2 weeks after study inclusion. Only 1 of these patients returned with symptoms compatible with uncomplicated malaria. The remaining 4 patients were routinely found to be positive at day 14 of follow-up. A recent study from Ghana that used RDTs also suggests no clinical harm in withholding antimalarial treatment from children with fever who have negative RDT results. However, evidence of the safety of withholding antimalarial treatment in this trial is limited, because >50% of patients with negative RDT results were still treated with antimalarials [10].

Taken together, the study from Tanzania [1] and the previous findings from Zanzibar [12] suggest that whereas RDTs will miss some clinically uncomplicated malaria infections, these are probably mainly low-density infections. Probably, some of these non–malaria-treated infections will be self limiting. Some patients will reattend with remaining uncomplicated clinical manifestations, but only rarely will they have developed into severe malaria manifestations. However, and importantly, the number of patients in the 2 studies is small, and therefore larger studies are needed to better quantify the potential risks of missed untreated malaria infections with serious health implications following false-negative RDT results. Among such future studies incorporating RDT in integrated management of childhood illness, optimally some should include details on how antibiotic prescriptions are affected by RDT results. In turn, this may be related to investigations on etiological causes of the fever episodes and thus may provide important insights into the clinical benefits of improved treatment of alternative fever causes.

In conclusion, the present study by d'Acremont et al [1] provides evidence of safety and support of the new paradigm in management of febrile children at the peripheral health care level in Sub-Saharan Africa, namely improved targeting of antimalarial treatment based on parasitological diagnosis and, more specifically, based on the use of RDT in this context. However, additional and larger studies are needed, in different malaria epidemiological settings and at different health care levels, that include data on health outcome, nonmalaria etiologies, and treatments, and that have longer follow-up. Importantly, if these studies are performed under ordinary health care conditions, they may provide the evidence required for optimal use of guidelines for integrated management of childhood illness in Africa.

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