To the Editor—We would like to complement Walker et al. [1] on their informative review article on CNS parasitic infections in immunocompromised hosts. However, there is a statement and a table regarding the diagnosis of malaria using serological tests and rapid malaria tests that is misleading and deserves clarification. This is particularly important, because the submission package for the first rapid malaria test that may be approved in the United States is nearing completion. Walker et al. state that the “[s]erological tests (ParaSight-F and Immunochromatographic Malaria P[lasmodium] falciparum test) are available, but false-positive test results are common” [1, p. 118]. Table 3 on page 117 of their article makes a similar statement and also indicates that the specimen type for the ParaSight-F (Becton Dickinson) and Immunochromatographic tests is a serum sample.

It is important to distinguish serological tests and antigen detection tests and the appropriate specimen type for these assays. Serological assays (for the detection of anti-malarial IgG and IgM in patient serum) have limited clinical utility for the diagnosis of malaria [2]. Most individuals who have resided in areas of moderate or high endemicity for malaria will demonstrate a persistent antibody response. On the other hand, several rapid malaria tests based on the detection of malaria antigens in whole blood samples, such as parasite histidine-rich protein II, aldolase, and lactate dehydrogenase, are available on the global market (however, as far as we know, ParaSight-F is no longer manufactured). These newer-generation assays display high sensitivity and specificity for acute clinical P. falciparum infections, with more variable results for infection due to non-falciparum species of Plasmodium [3–6].

A pivotal clinical trial evaluating the performance of the NOW ICT (Binax) rapid antigen test in >4000 patients was recently presented at the American Society of Tropical Medicine and Hygiene Annual Conference in Washington, D.C., in December 2005 by the US Army [7]. Overall sensitivity and specificity were 95% and 94%, respectively, for P. falciparum infection and 69% and 99%, respectively, for Plasmodium vivax infection. For parasitemia counts of >5000 parasites/μL, sensitivity was >99% for P. falciparum infection and 94% for P. vivax infection. In addition, the authors state “false-positive test results are common” [1, p. 117]. In many instances, “false-positives” are seen because the rapid test is more sensitive than routine microscopic examination (with histidine-rich protein II–based tests) or because anti-gamma globulins persist for a few days after clearance of parasites. True false-positive test results (i.e., instances in which the rapid test result is positive, but the patient does not have malaria) are much less common in field use. Occasional false-positive results have been seen in patients with a positive rheumatoid factor with some test kits [8]. It is important for infectious disease specialists to understand the appropriate sample type, properties, clinical utility, limitations, and performance characteristics of diagnostic tests for this important disease.

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References


Reply to Stauffer et al.

To the Editor—We thank Drs. Stauffer, Magill, and Kain [1] for providing clarification regarding rapid malaria tests, and we agree that it is important for health care workers to understand the appropriate sample types and performance parameters of diagnostic tests. In our article [2], we erroneously stated that the appropriate specimen type for rapid malaria tests was serum rather than whole blood. We agree that serological tests for malaria are of limited clinical value.

Rapid malaria tests are easy to use and require little training to interpret the results, but they are not as sensitive as traditional microscopy of thick and thin blood smears or PCR assay [3]. The ParaSight-F test for malaria detects histidine-rich protein II antigens in whole blood, but it is no longer manufactured. The NOW ICT rapid test (Binax) for malaria detects histidine-rich protein II antigens and an aldolase antigen common to Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, and Plasmodium malariae. Although this and other rapid malaria tests are highly sensitive when the level of parasitemia is $>1000$ parasites/μL, the sensitivity falls to 55%–68% for parasitemia with a level of 100–1000 parasites/μL [4, 5]. In a study conducted in Canada, 26.5% of patients with malaria had $\leq 1000$ parasites/μL [4]; in a study conducted in England, 17.3% of patients with malaria had $<500$ parasites/μL and 43.3% had $\leq 5000$ parasites/μL [6]. Thus, low levels of parasitemia are not uncommon, and the diagnosis of malaria cannot be excluded on the basis of a negative rapid test result. We agree that false-positive results with rapid tests are uncommon, with specificity varying between 95% and 99% [4, 5, 7].

At a recent meeting of the World Health Organization to discuss rapid malaria tests, none of the experts were aware of any published trial that examined the sensitivity and specificity of the rapid tests in persons with HIV infection (R. Peeling, personal communication). As mentioned in our article [2], the intensity of parasitemia is greater among HIV-uninfected adults than it is among HIV-uninfected children, and it increases with advanced immunosuppression [8–12]. In Malawi, the median parasite density was 1725 parasites/μL [13]. Quantitative studies of parasitemia in HIV-infected pregnant women have reported mean parasite densities of 757–4390 parasites/μL [9, 14, 15]. In contrast to the elevated intensity of parasitemia observed in HIV-infected adults, parasitemia in HIV-infected children appears to be equal to or lower than the intensity found in uninfected children [16–19]. Because parasitemia appears to vary in intensity according to HIV serostatus and age, the sensitivity of the rapid malaria tests may also vary.

The benefit of rapid tests for malaria is greatest in countries where laboratories are not equipped to perform blood smears or where technicians are not experienced with light microscopy of thick and thin blood smears [3]. In addition, as Kain et al. [20] noted, in Canada, the average delay between ordering blood smears for malaria and receiving results is 3 days; rapid tests can reduce this delay to minutes and provide a valuable diagnostic tool for the physician confronted with a potential case of malaria. We look forward to reading additional information regarding the performance characteristics of rapid malaria tests in immunocompromised hosts.

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References