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False Positivity of Rapid Antigen Detection Tests for Diagnosis of *Plasmodium falciparum* Malaria: Issue Appears To Be More Complicated than Presented

We read with interest the letter by Mishra and colleagues (3) suggesting that cross-reactions with rheumatoid factor (RF) that lead to false-positive results with *P. falciparum* rapid antigen detection tests are a problem confined to the ParaSight-F test (Becton Dickinson, Cockeysville, Md.) only. However, it appears to us that the issue is more complicated than hypothesized by Mishra et al., because their data were derived from a sample size which might have been too small.

As previously described in detail, in a series of 91 RF-positive, malaria-negative specimens, Grobusch et al. (1) found an overall false-positivity rate of 19.8% (18 of 91 specimens) with three different test systems based on the detection of two different plasmodial antigens. Whereas both ParaSight-F and ICT Malaria P.f. (ICT Diagnostics, Sydney, Australia) detect plasmodial histidine-rich protein 2 (HRP-2), OptiMAL (Flow Inc., Portland, Oreg.) detects parasite-specific lactate dehydrogenase (4). Although the problem appears to be most pronounced with the ParaSight-F test (15 of 91 specimens [16.5%]), we found false positives with the ICT Malaria P.f. (6 of 91 specimens [6.6%]) and the OptiMAL (3 of 91 specimens [3.3%]) tests as well.

Mishra et al. explain their findings by arguing that RF is incapable of binding to immunoglobulin M (IgM)-type capture monoclonal antibody, which is used in the ICT test. We are skeptical about this conclusion on the grounds that RF has previously been described to interfere with various test systems by inducing false-positive reactions for specific IgM antibodies in some parasitic and other infectious diseases (2). Based on our findings we assume that, although to varying extents, all currently available rapid immunochromatographic malaria tests may lead to false-positive results due to cross-reaction with RF.

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Authors' Reply

Two observations by Grobusch et al. (3) are not supported by the available literature (1, 2, 5, 6). (i) The rate of false positivity with the ICT test in their study is higher (6 of 91 specimens [6.6%]) than those in other studies (0 of 23 specimens and 0 of 25 specimens [described in references 1 and 6, respectively]). (ii) The rate of false positivity with the ParaSight F test in their study is significantly lower (15 of 91 specimens [16.5%]) than those in other studies (60% to 83% [described in references 1, 2, 5, and 6]).

Hence, their result may not be acceptable till other studies support the discrepancies in authors' observations on the rates of false positivity of these two tests. Considering the findings of our study (6) as well as those of the study of Bartoloni et al. (1), it is evident that false positivity was found only with the ParaSight F test and not with the ICT test.

We can offer no comments on false positivity with the OptiMAL test as we have not performed that test. However, we would like to know whether IgG or IgM antibody is coated onto the strips. Immunochromatographic tests in which IgG antibody is used as the coating antibody to capture HRP-2 antigen are likely to give higher rates of false positivity (ParaSight F test) than a test system in which IgM antibody is coated onto the strips (ICT test). All available literature, including the authors' study (3), supports this observation.

The reference quoted by the author (4) regarding the false positivity due to RF in various parasitic and other infectious diseases simply mentions "a number of studies concerned with detection of IgM antibodies to infectious agents have shown that IgM RFs may interfere in the tests and cause false-positive reactions since RFs may react secondarily with IgG which is bound to the primary antigen in the test system." Therefore, it does not contradict but instead supports our statement that RF leads to false positivity in the ParaSight F system because it binds to IgG. As described in our paper (6), the capture antibody in the ParaSight F test is IgG, and that in the ICT system it is probably IgM in nature. So, it is quite logical to hypothesize that the binding of RF to IgG is one of the reasons for false positivity.

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