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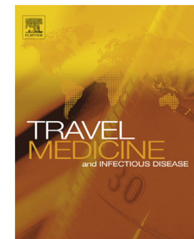

False-positive rapid plasma reagin testing in patients with acute *Plasmodium vivax* malaria: A case control study☆,☆☆

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Summary Non-treponemal tests such as the rapid plasma reagin (RPR) assay are mainstays of syphilis diagnosis, but false-positive tests are common. We identified false-positive RPR titers in 8.2% of patients with malaria due to *Plasmodium vivax* in northern Peru. Similar rates were not detected in patients with other acute febrile illnesses.
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Introduction

The prevalence of syphilis has increased greatly over the past decade, with an estimated worldwide prevalence of 12 million cases, of which 90% are believed to occur in developing countries [1]. The diagnosis of syphilis is complicated by the inability to culture its causative agent, *Treponema pallidum pallidum*, and by the protean nature of its symptoms. The sequelae of untreated syphilis make early treatment paramount. *T. pallidum* has defied vaccination and eradication efforts, despite the effectiveness and availability of benzathine penicillin as first-line treatment. In Peru, 0.4—0.5% of young Peruvian adults have serologic evidence of syphilis infection [2]. The lesions of symptomatic early syphilis are associated with increased

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transmission of human immunodeficiency virus (HIV) and other sexually transmitted infections, partially due to erosion of mucosal genital surfaces [3].

The detection of syphilis is complicated by frequent false positives on screening tests in patients with inflammatory disorders. The rapid plasma reagin (RPR) is the most commonly used screening test for blood, while the Venereal Disease Research Laboratory (VDRL) is used to screen both blood and cerebrospinal fluid (CSF) specimens. Both assays detect nonspecific antibodies to host cardiolipin antigens, and as such are referred to as non-treponemal assays. Positive RPR and VDRL results are confirmed with a more specific treponemal assay, such as the *T. pallidum* hemagglutination (TPHA) or fluorescent treponemal antibody-absorption (FTA-ABS) tests, which measure specific antibodies to treponemal antigens and differentiate true from false-positive RPRs or VDRLs. Recently, the syphilis diagnostic algorithm has come under reconsideration, with some organizations considering the use of treponemal tests as an initial screening tool, to be followed by RPR or VDRL to estimate disease activity and severity [4]. The main motivation for this is cost and automation, as the RPR and VDRL assays are manual tests whereas the newer treponemal enzyme immunoassays (EIAs) can be run on automated instruments.

The RPR was used as a screening tool in a recent collaboration between the Naval Medical Research Center (NMRC, Silver Spring, Maryland) and Naval Medical Research Unit No. 6 (NAMRU-6, Lima, Peru) as part of ongoing studies of acute febrile illness and *Plasmodium vivax* infection in northern coastal Peru.

After providing informed consent, blood from patients with acute vivax malaria was offered to female anopheline mosquitos through an *in vitro* feeding apparatus; the mosquitoes were shipped to NMRC for analysis and use in human *P. vivax* challenge model development. Infected donors in Peru were screened for bloodborne infections as part of their enrollment, including testing for HIV, hepatitis B and C, and syphilis. In the course of this study, patients with active vivax malaria were observed to have a disproportionate frequency of positive RPRs on screening serologies. Confirmatory testing with TPHA demonstrated these positive RPRs to be false positives. Similar false positives were not demonstrated in the control population, who were Peruvian adults with non-malarious febrile illnesses. Based on this observation, a case—control study of RPR reactivity was conducted to quantify this phenomenon in acutely febrile patients with and without vivax malaria.

Methods

These studies were conducted following ethical review and approval by the Peruvian Ministry of Health and by the Institutional Review Boards of NMRC and NAMRU-6, in accordance with United States Federal and Peruvian regulations for the protection of human subjects (protocols NMRCD.2008.0004, NMRCD.2000.0006, and PJT.NMRCD.068). Patients were offered enrollment into an ongoing febrile surveillance project in the cities of Tumbes and Sullana, in northern coastal Peru, upon presentation to an affiliated health center with an undifferentiated fever of $\geq$38.0 °C for $\leq$7 days.

Upon obtaining informed consent, patients were initially evaluated for malaria by microscopy and then later confirmed by PCR [5]. Parasite density was calculated by counting the number of asexual parasites per 200 white blood cells in the thick smear, assuming a mean white blood cell count of 6000 per μL. Seventy-three patients with malaria, all with *P. vivax* infection, were identified; no cases of falciparum malaria were diagnosed in this sample. In patients without malaria, serum specimens were tested by viral culture and PCR for arboviral pathogens as well as by paired acute and convalescent IgM ELISA for viral antibodies [6]. A sequential sample of 76 such patients was selected from the same time period and geographic region as the patients with malaria to serve as controls. Testing with RPR (RPRnosticon II kit, bioMérieux, Marcy l'Etoile, France) and TPHA (TPHA 100, bioMérieux) was then performed on all samples.

A confirmed case of syphilis was defined as an RPR titer $\geq$1:1 with a positive TPHA result. All positive results, including syphilis diagnoses, were communicated with patients and attending clinicians in order to provide appropriate therapy. Groups were compared for significance by two-tailed Fisher's exact test or *t*-test, as appropriate. Significance was defined as a p-value of $\leq$0.05.

Results

Demographics and test results for patients with malaria and for febrile controls without malaria are presented in Table 1. Those patients with malaria were more likely to be male and were slightly older than malaria-uninfected controls, but these differences did not achieve statistical significance. Positive RPR titers were detected in 8/73 (11.0%) patients with malaria. Of these, 2/73 patients (2.7%) with malaria had a positive TPHA consistent with syphilis, while 6/73 (8.2%) patients had false-positive RPR titers. All six of these patients were men; no false-positives were detected in women in the sample. False-positive RPR titers ranged from 1:1 to 1:16 (Table 2). A positive RPR titer was detected in 1/76 (1.3%) of patients without malaria; this single patient had a positive TPHA confirming syphilis. No false-positive RPRs were detected among the control group. No blood type differences were observed between groups. No significant differences in degree of parasitemia were noted in malaria-infected participants with and without false-positive RPRs.

Discussion

Prior to advent of penicillin, therapeutic infection of patients suffering from neurosyphilis with *Plasmodium* was conducted to induce fever with the intention of denaturing spirochetal proteins [7]. Since the introduction of penicillin, the hazardous work and uncertain results of malariotherapy were rapidly supplanted by more effective antimicrobial therapy, but observations of the serologic effect of malaria on syphilis diagnostics date from this period. The phenomenon of false-positive RPRs in patients with malaria was described in the 1930s and 1940s in both natural and experimental infections. Between 2 and 4% of European patients in Africa with treated, naturally-

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