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Therapeutic efficacy of chloroquine and chloroquine plus primaquine for the treatment of *Plasmodium vivax* in Ethiopia

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ABSTRACT

Plasmodium vivax is the second most important cause of morbidity in Ethiopia. There is, however, little information on *P. vivax* resistance to chloroquine and chloroquine plus primaquine treatment although these drugs have been used as the first line treatment for over 50 years. We assessed the efficacy of standard chloroquine and chloroquine plus primaquine treatment for *P. vivax* infections in a randomized open-label comparative study in Debre Zeit and Nazareth in East Shoa, Ethiopia.

A total of 290 patients with microscopically confirmed *P. vivax* malaria who presented to the outpatient settings of the two laboratory centers were enrolled: 145 patients were randomized to receive CQ and 145 to receive CQ+PQ treatment. Participants were followed-up for 28–157 days according to the WHO procedures. There were 12 (6.5%) lost to follow-up patients and 9 (3.1%) withdrawals. In all, 96% (277/290) of patients were analysed at day 28. Baseline characteristics were similar in all treatment groups. In all, 98.6% (275/277) of patients had cleared their parasitemia on day 3 with no difference in mean parasite clearance time between regimens (48.34 ± 17.68, 50.67 ± 15.70 h for the CQ and CQ+PQ group, respectively, $P = 0.25$). The cumulative incidence of therapeutic failure at day 28 by a life-table analysis method was 5.76% (95% CI: 2.2–14.61) and 0.75% (95% CI: 0.11–5.2%) in the CQ and CQ+PQ group, respectively ($P = 0.19$). The relapse rate was 8% (9/108) for the CQ group and 3% (4/132) for the comparison group ($P = 0.07$). The cumulative risk of relapse at day 157 by a life-table method was 61.8% (95% CI: 20.1–98.4%) in the CQ group, compared with 26.3% (95% CI: 7.5–29.4%) in the CQ+PQ group ($P = 0.0038$).

The study confirms the emergence of CQ and PQ resistance/treatment failure in *P. vivax* malaria in Ethiopia. Although treatment failures were detected, they were similar between the treatment groups. We recommend regular monitoring and periodic evaluation of the efficacy of these antimalarial drugs in systematically selected sentinel sites to detect further development of resistance and to make timely national antimalarial drug policy changes.

1. Introduction

Plasmodium vivax is the most prevalent malaria infection and is an important cause of morbidity in many endemic regions in the world, especially in Asia, Central and South America. An estimated 70–80 million clinical vivax malaria episodes occur worldwide each year (Mendis et al., 2001). Recent global estimates, however, suggest that *P. vivax* infects around 130–435 million people per year (Baird, 2007; Price et al., 2007). About 10–20% of the global burden of vivax malaria occurs in Africa, especially in Eastern and Southern African countries. Infections during pregnancy have also been associated with maternal anemia and low birth weight (Nosten et al., 1999). More recently, severe and fatal malaria associated with *P. vivax* and with mixed infections of both vivax and falciparum

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malaria have been reported from several endemic countries, mainly from Asia (Barcus et al., 2007; Baird, 2007; Price et al., 2007; Tjitra et al., 2008; Genton et al., 2008). In Ethiopia, *P. vivax* is the second most important causes of morbidity, accounting for about 30–40% of the total annual 5–6 million reported malaria cases (approximately 1.5–3 million cases per year) (MoH, 2004a). The disease is highly prevalent in mid and high altitude areas with low-to-moderate transmission. The disease is also more common during dry or low transmission seasons probably attributable to relapse (Tulu, 1993). Patients with *P. vivax* infections usually experience 3–5 relapses even if each clinical attack is treated, with the first relapse occurring between 3 and 10 months after the initial treatment (Schwartz and Regev-Yochay, 1999; Schwartz et al., 2000).

Chloroquine (CQ) and primaquine (PQ) have been used as the first line therapy for clinical vivax malaria infections for over 50 years in most endemic countries in the world. However, CQ-resistant *P. vivax* has emerged in Oceania, South East Asia (Rieckmann et al., 1989), and more recently has become reported from several endemic regions in Asia and South America (Baird et al., 1991, 1997a,b; Ruebush et al., 2003; Baird, 2004). PQ has been known to potentiate the efficacy of CQ against asexual stages and to prevent relapse by killing hypnozoites (Pukrittayakamee et al., 1994; Wilairatana et al., 1999; Baird and Hoffman, 2004). Nevertheless, resistance to or tolerance of PQ by *P. vivax* has been documented in Somalia in East Africa, and South East Asia (Smoak et al., 1997; Looareesuwan et al., 1997; Collins and Jeffery, 1996; Wilairatana et al., 1999; Baird and Hoffman, 2004).

In Ethiopia, CQ combined with PQ has been used as the standard treatment for *P. vivax* infections for more than five decades. CQ is administered at a dose of 10 mg base/kg on days 0 and 1, and 5 mg base/kg on day 2. PQ is administered at a dose of 0.25 mg base/kg daily for 14 days to achieve a radical cure, particularly in areas where there is less risk of re-infection. However, this PQ treatment regimen has been limited to 3–5 days in areas where there is high risk of re-infection, primarily to reduce the risk of transmission (MoH, 1999). In 1999, CQ had become replaced with Sulfadoxine/Pyrimethamine (SP) for the treatment of uncomplicated falciparum malaria due to high rates (65%) of CQ resistance or treatment failures (MoH, 1999; WHO, 2005). In 2004, SP was again replaced with Artemether-Lumefantrine (ART-LUM) due to high rates (35%) of SP treatment failures (Jima et al., 2005; MoH, 2004a,b). There is, however, little information on the response of *P. vivax* to CQ and CQ + PQ treatment. In a study conducted from Debre Zeit area in 1996, the rate of parasitological failure to CQ treatment on day 7 was indicated to be 2% ($n = 255$) (Tulu et al., 1996) although this report failed to identify the presence or absence of mixed infections or to indicate the effect of PQ treatment on vivax malaria. As a result, the standard treatment for *P. vivax* infections remains unchanged. The current national malaria treatment guideline recommends the use of CQ or CQ + PQ in combination with ART-LUM for the treatment clinical vivax malaria infections in the absence of definitive diagnosis (MoH, 2004a,b), which increases the cost of treatment. In this study, we primarily assessed the efficacy of standard CQ and CQ + PQ treatment for *P. vivax* infections in a randomized open-label comparative study in patients who presented to the outpatient settings of the Debre Zeit and Nazareth malaria laboratory and treatment centers in East Shoa, Ethiopia. In addition, we evaluated the risk of relapse after patients had cleared their primary infections and resolved clinical symptoms.

2. Materials and methods

2.1. Study areas

The study was conducted between January and August 2003 at the outpatient settings of the Malaria Diagnosis and Treatment Centers in Debre Zeit (located at latitude 8.746° N, longitude 38.967° E; altitude, 1900 m) and Nazareth (located at latitude 8.535° N, longitude 39.27° E; altitude, 1622 m), East Shoa, Central Ethiopia (Fig. 1). Transmission in these study sites is largely seasonal and unstable, with peaks from September to December and from April to June. Diagnosis and treatment services of malaria are provided

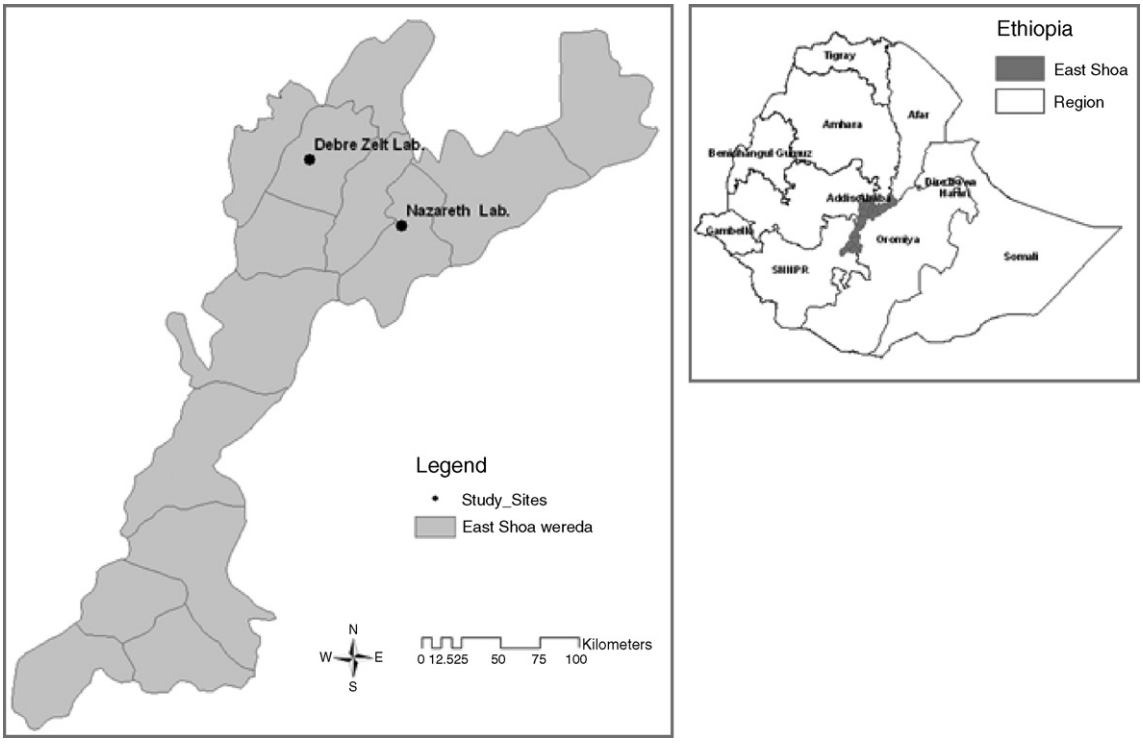

Fig. 1. Location of the study sites, East Shoa, Ethiopia.