The neglected *Plasmodium vivax*: are researchers from endemic areas really concerned about new treatment options?

O *Plasmodium vivax* negligenciado: os pesquisadores de áreas endêmicas estão mesmo preocupados com novas opções de tratamento?

Dear Editor:

The global burden of malaria caused by *Plasmodium vivax* is approximately 80 million cases annually. Outside Africa, *Plasmodium vivax* accounts for more than 50% of all malaria cases, with the majority (80-90%) occurring in the Middle East, Asia and the Western Pacific, and 10-20% in Central and South America[7]. It is usually considered to be a benign disease; however, there are reports of increasing clinical severity[5,6] and resistance to antimalarials[1,2,8] in South America and Southeast Asia. If mortality due to malaria is not an issue of priority in *Plasmodium vivax* endemic areas, then attention should be given to the absenteeism from work and school and the anemia that this disease produces, which certainly impairs the sustained development of these areas[11]. The highly significant economic impact of *Plasmodium vivax* malaria mandates that more resources be directed specifically to research on this parasite, including studies on pathogenesis and drug resistance.

Figure 1 shows the number of controlled, randomized clinical trials with antimalarials for *Plasmodium falciparum* or *Plasmodium vivax* on the respective continent where the study was conducted, from January 1996 to December 2005, identified through MEDLINE (key words searched in the MeSH database: malaria, *vivax; Plasmodium vivax*; malaria, f*alciparum*; *Plasmodium falciparum*; therapeutics; therapy; treatment outcome; treatment failure; clinical protocols; therapies, investigational). Only 31 studies were performed with antimalarials for *Plasmodium vivax* over this 10-year period. Surprisingly, most of the articles published in Asia and the Americas, where *Plasmodium vivax* is more common than *Plasmodium falciparum*, relate to antimalarials for treating *Plasmodium falciparum*.

Chloroquine is still the drug of choice for treating *Plasmodium vivax* malaria around the world. The increasing resistance to this drug has not yet led to any studies on the schizonticidal drugs that are used routinely for *Plasmodium falciparum*, as

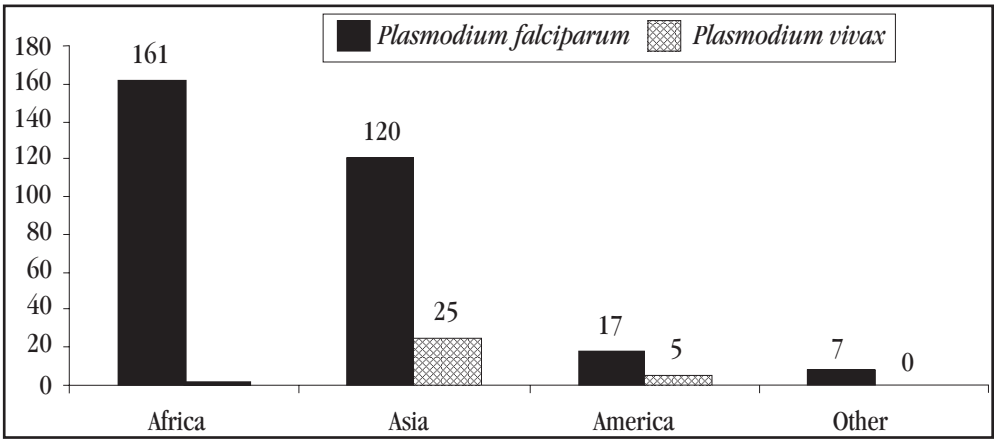

Figure 1 - Number of published controlled randomized clinical trials on antimalarials for* Plasmodium falciparum *and Plasmodium vivax, from 1996 to 2005 (MEDLINE), according to the continent on which the study was conducted.

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potential alternatives for *Plasmodium vivax*. Chloroquine was developed in 1934, is very cheap (US$ 0.10 per treatment) and easy to administer, and has few side effects. Nonetheless, new drugs and therapeutic schemes are needed to treat the growing number of patients who cannot be cured with chloroquine[9]. Artemisinin-based combination therapy (ACT) has been strongly recommended by the World Health Organization for treating *Plasmodium falciparum*. Systematic testing against *Plasmodium vivax* should also be considered in order to simplify treatment schemes and/or evaluate ACT as an alternative when resistance emerges and becomes widespread.

Artesunate plus mefloquine is a highly effective combination against resistant *Plasmodium falciparum*[4] and is under field investigation in Brazil. Artemether plus lumefantrine has already been adopted as the first-line option for non-severe falciparum malaria treatment in some Brazilian endemic areas since 2006. These ACTs may provide not only an effective alternative for treating this often lethal parasite, but should also be considered highly relevant in relation to the emergence of *Plasmodium vivax*, among countries that are committed to decreasing malaria morbidity in the Americas.

Radical cure for *Plasmodium vivax* malaria (by killing the hypnozoites) is achieved only with primaquine. In cases of resistance to this drug or when contraindications such as G6PD deficiency exist, no other drug is available. Tafenoquine is a promising new 8-aminoquinoline that still needs additional Phase III clinical trials[10] and regulatory approval. The lack of a good *in vitro* protocol for *Plasmodium vivax* cultivation, which may also unfortunately be regarded as having been a non-priority issue in recent years, immensely restricts the preclinical development of additional new drugs against this parasite.

The declining efficacy of current therapies for *Plasmodium vivax* highlights the need for new treatment options. Underestimating the impact of *Plasmodium vivax* on the global health system may dramatically impair the achievement of one of the 2015 United Nations Millennium Development Goals, i.e. a commitment to *have halted and begun to reverse the incidence of malaria and other major diseases* by that date (http://www.un.org/millenniumgoals/).

Malaria, as a single entity, is recognized as a prominent neglected disease, without much research and development investment devoted to it. However, most of the activity is perhaps justifiably focused on *Plasmodium falciparum*, because of its more lethal consequences. Nevertheless, the important health and economic morbidity that *Plasmodium vivax* imposes upon a much larger number of people in certain areas requires committed support for baseline mapping of its prevalence, new scientifically proven treatment protocols, and appropriate alignment of research efforts with regional and national health policies[3].

In our view, the serious risk posed by *Plasmodium vivax* malaria in endemic areas is not fully recognized and acknowledged. Only 31 *Plasmodium vivax* drug studies reported over a 10-year period illustrates the poor level of interest in this vital area. This particular malarial species may become a much more prominent neglected disease in the immediate future if specific *Plasmodium vivax* research is not greatly enhanced.

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