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Scientific comment

We need to talk more about transfusion-transmitted malaria in *Plasmodium vivax* endemic areas☆

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Malaria is the most widespread and relevant parasitic disease worldwide; it is primarily transmitted by bites of *Anopheles* sp., but can also be transmitted congenitally or through infected blood transfusions. The major species infecting humans are *Plasmodium falciparum* and *P. vivax*. Even considering that both species lead to severe disease, the first has been traditionally associated to more deaths, mostly in the African continent. No vaccine is available so far and the major control tools are based on early diagnosis and treatment, and vector control.

In Brazil, after the eradication campaign started in the 1950s, malaria became restricted to the Amazon Region, which despite representing 50% of the national territory holds no more than 10% of the population. After the 1990s, due to better control of *P. falciparum*, *P. vivax* became the main species, and is responsible for almost 85% of the reported cases, paralleling the decrease in the overall fatality rate, the most successful goal of the Brazilian Malaria Control Program.[1] However, this parasite is able to develop dormant stages (hypnozoites) in the liver leading to frequent relapses, thereby confounding officially reported data, since it is not possible to distinguish new infections from relapse. With renewed interest in malaria eradication in 2007, *P. vivax* became a significant challenge as no good tools are available to tackle hypnozoites and therefore, relapse.[2] In this context, uncommon ways of transmission regain attention, such as transfusion-transmitted malaria, which is capable of reintroducing the parasite in an area moving toward its elimination.

It is doubtless that transfusion-transmitted *P. falciparum* malaria is a real danger to a patient, who may develop severe disease and die. However, in areas such as the Amazon region, where *P. vivax* predominates, there is a general consensus, due to the misleading information that vivax malaria is more benign, that transfusion-transmitted malaria is not so problematic and therefore not much public health attention is given to this scenario. Recent data conclusively show that *P. vivax* is actually associated to severe disease,[3] namely

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amongst patients with comorbidities, which fits precisely the characteristics of blood transfusion recipients. Taking this into account, it is possible that both vivax and falciparum endemic areas deserve similar attention regarding the control of this healthcare associated infection.

Other specific characteristics of *P. vivax* which make control of transfusion-transmitted malaria even more complicated are: (1) faster acquisition of immunity, leading to more asymptomatic cases that cannot be detected during epidemiological screening in blood banks; (2) as *P. vivax* infects only reticulocytes, parasitemia is usually low and therefore, less likely to be detected by the routine thick blood smear examination; (3) frequent multiple relapses are detected essentially through active case searches because clone-specific immunity leads to asymptomatic relapse; (4) chloroquine resistance (including reports from the Brazilian Amazon) is able to extend periods of asymptomatic low parasitemia after beginning treatment.[2] Thus, donors implicated in this kind of transmission are often semi-immune, and with parasite levels below the detection threshold of currently available assays at blood banks. Furthermore, in many endemic areas in Latin America, malaria is becoming a disease of peri-urban areas, where the population has been concentrated (rural exodus).[4] This epidemiological transition takes Plasmodium carriers closer to the urban blood banks, enabling more and more donations of contaminated blood.

The dichotomy of this issue focuses either on the infection of the blood recipient if a less sensitive method is used for Plasmodium screening, or on insufficient blood stocks if a more rigid approach is adopted. In general, transfusion-transmitted malaria does not call the attention of national authorities. Since 2002, official data from Brazil reported only four cases. Whether the very low number of cases is due to under-reporting or not, is an issue that needs to be addressed. There is no clear policy on the following up of blood recipients in the Amazon, and since most of them already live in endemic areas, new infections may not necessarily be reported as transfusional. No matter what strategy is adopted to prevent transfusion-transmitted malaria, it is likely that this kind of transmission may still occur, and so malaria must always be considered in any patient with a post-transfusion febrile illness.

In the non-Amazon area of Brazil, the policy is clear: no patient coming from an endemic area is accepted as a donor. However, recent data point to the occurrence of Plasmodium positive blood in blood banks from the Brazilian Southeast.[5] If these samples come from travelers or from patients in contact with the Atlantic Forest, where autochthonous Plasmodium is occasionally found, is still a matter of debate.

In the Amazon area, epidemiological screening of potential donors has been traditionally adopted. Patients reporting a confirmed malaria infection in the past six months have their donation declined, as well as patients coming from municipalities with an annual parasite index (API) higher than 49 cases/10,000 inhabitants.[6,7] Moreover, since no quantitative buffy coat test (QBC), a more sensitive technique based on the search of parasites stained with a fluorescent dye in the concentrated buffy coat, is available, some centers perform the routine thick blood smear microscopy evaluation in all samples. The major problems with this screening strategy is that asymptomatic *P. vivax* relapses may occur even after six months of the primary infection;[2] API, despite being reliable in Brazil, is not uniform throughout the whole municipality and changes considerably from one year to the next (on-line updated official data are not available to blood banks); the thick blood smear is not as sensitive as to allow a proper detection of low parasitemia in asymptomatic patients, and the use of rapid diagnostic tests is not different.

In the timely paper published by Freitas & Duarte in this issue of the Revista Brasileira de Hematologia e Hemoterapia,[8] the first extensive evaluation of nine blood banks from the Brazilian Amazon point to non-uniform and imprecise adopted practices. The standardization of national policies is urgent and the evaluated impact of these policies needs to be shared with similar endemic areas throughout the world.

Maybe this is the right time to address more aggressive measures in the elimination of transfusion-transmitted malaria, as part of a joint strategy to eliminate malaria from endemic areas.[9] The first and most important thing to do is to estimate the real burden of transfusion-transmitted malaria. Therefore, better surveillance is urgently needed, both in the many malaria diagnostic posts spread throughout the Amazon region and in blood banks. Screening for a recent blood donation is recommended in malaria services. In blood banks, thick blood smears are probably not the best diagnostic tool for asymptomatic donors even if the number of read fields in microscopy is increased, because it is time-consuming and presents low sensitivity for this purpose. Many studies have suggested polymerase chain reaction (PCR) as a more sensitive tool to detect small concentrations of parasite DNA.[10] New techniques such as real-time PCR and loop mediated isothermal amplification (LAMP), with costs that have decreased in the last few years, would be ideal in blood banks.[11] Increasing the volume of blood for DNA extraction, and PCR performed in blood sample pools[12] are interesting strategies as well, however, the sensitivity of these techniques needs additional evaluation. Serological markers have been abandoned as a screening tool because of the low specificity, especially in endemic areas. However, new epitopes are being discovered as reasonably good markers of the asymptomatic population in the Amazon.[13] These more specific markers need to be addressed in blood banks, because of their lower costs compared to PCR and because they are compatible with similar serologies already performed for other infectious diseases in these settings. Furthermore, new methods are needed to ensure transfusion safety without rejecting potential donors, which would ensure safe transfusion without harming the blood supply.[14] Not a long time ago, gentian violet was added to the blood to control transfusion-transmitted Chagas' disease. The action against Plasmodium seems to be similar,[15] but gentian violet has never been studied for this purpose. The effects of gentian violet (with action against other parasites such as Toxoplasma, Trypanosoma and Leishmania or even a wide spectrum) and the safety of antimalarial drugs on blood components need to be revisited.

Malaria is under control in most of Latin America, however, a new challenging goal is its elimination. Thus, all possible transmission routes need to be interrupted. In theory, not many private blood banks exist in the Brazilian Amazon, which would make them the perfect scenario to test new

strategies in terms of effectiveness and efficiency. That would substantially add information to a neglected problem in most *P. vivax* endemic areas.

Conflicts of interest

The authors declare no conflicts of interest.

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