Editorial

The Importance of Being vivax

Plasmodium vivax is indisputably the most widely distributed cause of human malaria, and the prevailing species outside of Sub-Saharan Africa [1], putting over one-third (2.5 billion people) of the globe’s population [2] at risk every year, and causing an estimated 80–300 million annual clinical episodes [3]. Plasmodium vivax is heterogeneously scattered in the different continents, with over 80% of the total global burden unevenly circumscribed to the Pacific and central and south-east Asia [1, 2]. In America, the total burden is significantly lower, but this species still causes over 70% of all malaria episodes. In Africa, the high prevalence of the Duffy-negative genotype (inherently associated with a refractoriety to P. vivax invasion, and thus the major genetic determinant of its distribution [4]) has traditionally contained the dissemination of this species which is only frequently described in some areas of the horn of Africa and the Madagascar island, despite increasing reports of its circulation and transmission across the continent [5, 6].

Despite such robust evidence on this parasite’s burden and impact, efforts devoted in the past decades to the understanding and control of P. vivax have been meagre, particularly in comparison with those made for its sibling species Plasmodium falciparum, the major cause of malaria-related deaths globally. A review of funds invested for malaria research from 2007 to 2009 confirmed that a mere 3.1% of all funding had specifically targeted P. vivax [7], and the imbalance in publications or bibliographical references addressing either of the two parasite species is equally astonishing (Fig. 1). However, the past decade has witnessed an important paradigm change regarding these disparities. Indeed, the scientific and global health communities appear to be slowly confronting the significant neglect suffered by this malaria species and are increasingly devoting more attention and funds to P. vivax research and control.

Several reasons may explain the recent and unexpected focus on P. vivax. First, increasing reports of severe or even life-threatening episodes involving P. vivax infections [8–10] have modified this parasite’s dogmatic ‘benign’ consideration [11]. Indeed, most malaria-endemic areas in which this parasite is transmitted have now confirmed that it can cause severe disease, on its own, as a mixed infection in combination with P. falciparum or as a triggering factor of complications in patients with other co-infections or underlying co-morbidities [12]. Our current capacity, through the use of molecular tools, to pick up vivax monoinfections and rule out coexisting falciparum infections that may have been sequestered in the microvasculature and thus invisible in peripheral blood slides, permits a better-quality description of the malaria cases and attribution of morbidity. Additionally, post-mortem studies [13, 14] have confirmed the capacity of this species to cause death in absence of any other possible explanation. But has P. vivax become, throughout the years, more virulent, or has our expertise in diagnosing improved together with our awareness regarding its potential to cause severe disease? Historical data, including those coming from the past centuries’ European endemic countries or from the malariotherapy studies to treat complications of tertiary syphilis [15] would support the argument in favour of the naturally benign and usually self-limited vivax-induced disease, unless accompanied with other conditions or left untreated. However, clinicians and policymakers need to be aware of the increasing attribution of severity to this parasite, sometimes comparable with that of P. falciparum [16, 17], and affecting all age groups, and particularly, in highly endemic areas, young children [18], so that adequate preventive measures can be quickly established.

A second reason for the unprecedented attention vivax is receiving lately has to do with its growing relevance in the context of the renewed malaria elimination efforts [19]. Certain biological features, particular to this species, pose unique challenges to the control of P. vivax, including its capacity to transmit to the next human, through the generation of gametocytes at early stages of infection, even prior to the beginning of clinical symptoms (and thus of any possible treatment), or its relatively lower parasitaemia (secondary to the preference of this parasite for young reticulocytes rather than full grown red blood cells) which often hinders diagnosis without affecting its transmissibility. Additionally, the hypnozoite and its ability to act as a source for unpredictable transmission and clinical symptomatology, and its unresponsiveness to most antimalarial drugs, further complicates any efforts to eliminate this parasite. Such resilience often implies that P. vivax is the ‘last parasite standing’ in areas where intensive control measures are put in place, and therefore, understanding how to specifically tackle it becomes imperative to achieve elimination.

What makes vivax so utterly fascinating is the fact that substantial knowledge gaps persist regarding its capacity to cause disease and the dynamics of its infection and interaction with the human host [3]. Little is known on something as fundamental as the pathobiology of the hypnozoite, or the frequency,
determinants and clinical implications of relapse [20]. Similarly poor seems our understanding of *P. vivax*'s pathophysiology, and the role that cytoadherence and sequestration, a fundamental characteristic of *P. falciparum*'s pathogenicity, may play in *vivax* severe disease [21, 22]. Relatedly, more research needs to be devoted to the understanding of the interactions of *P. vivax* with other malarial species, or co-infections with other microorganisms [23], and how such interactions may fuel severe disease. The recent discovery that *P. vivax* may utilize alternative mechanisms than the Duffy receptor for the invasion of the reticulocyte also shakes previous dogmas and requires in-depth studies to understand its public health implications [24]. While antimalarial drug resistance to chloroquine, the drug successfully used for its treatment for the past seven decades, has clearly been documented and increasingly reported from various regions of the world, important lacunae persist regarding the molecular mechanisms conferring resistance, in comparison to what is known for *P. falciparum* [25]. A detailed characterization of molecular markers of *P. vivax* resistance to antimalarial drugs and more insights into the hypothesis linking chloroquine resistance to severe disease [26] are urgently needed. Finally, the field of *vivax* research is inextricably linked to the study of glucose-6-phosphate dehydrogenase (G6PD) deficiency because of the hazardous haemolytic side effects of *vivax*’s radical cure with 8-aminoquinolines in patients with this common genetic disorder. Further understanding of this phenomenon, and better diagnostic tools to screen populations likely to receive these drugs in the context of individual treatment or mass drug administration within malaria elimination efforts are warranted, at least until new and safer drugs are available.

It seems clear that *P. vivax* has regained in recent years the prominence and importance that this parasite deserves. The field of *vivax* research is slowly flourishing and will surely provide in the next years some answers to many of the uncertainties aforementioned. The public health burden cumulatively caused by this parasite species throughout history warrants that it is finally, and for once, exposed outside of *P. falciparum*’s impervious shadow.

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References