Severe Vivax Malaria: Newly Recognised or Rediscovered?

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Malignant tertian” and “benign tertian” are terms that have long been used for two of the major diseases we recognise as malaria. The former is generally considered to be synonymous with Plasmodium falciparum and the latter with Plasmodium vivax infection. As the names “malignant” and “benign” suggest, the current dogma is that P. falciparum can be severe and life-threatening while P. vivax tends to be milder. However, two studies published in this issue of PLoS Medicine challenge this dogma.

The Two New Studies

Ric Price and colleagues present data from southern Papua, Indonesia, suggesting that malaria resulting from infection with Plasmodium vivax is associated with severe and life-threatening disease. In a study carried out in Papua New Guinea, Blaise Genton and colleagues show that Plasmodium vivax is associated with severe malaria.

Linked Research Articles

This Research in Translation discusses the following new studies published in PLoS Medicine:


In a study carried out in Papua New Guinea, Blaise Genton and colleagues show that Plasmodium vivax is associated with severe malaria.

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Abbreviations: G6PD, glucose-6-phosphate dehydrogenase; PvDBP, P. vivax Duffy binding protein

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Research in Translation discusses health interventions in the context of translation from basic to clinical research, or from clinical evidence to practice.
Control of malaria depends on effective strategies at the first line, elimination of liver stages, and preventive therapy. Other factors, such as host genetics, can also influence the differences in severe disease manifestation between study sites. It has been shown, for example, that children in Papua New Guinea with the red cell genetic polymorphism “South East Asian ovalocytosis”, a trait common in this population, are almost completely protected from cerebral malaria [6]. In Timika, indigenous Papuans were much more likely to be severely anaemic than were immigrants. Host genetics may contribute to the high anaemia rates reported in the Timika study.

Interactions between Vivax and Falciparum

There is a view that malarial disease severity in New Guinea may be lower overall than in Africa. For example, case fatality rates for *P. falciparum* among hospitalised children in New Guinea ranged from 1.6% to 3.5% [7,8] versus 2% to 9% in recent African studies [9–11]. This difference raises the question of whether *P. vivax*, which is common in New Guinea but rare in Africa, may actually ameliorate the severity of *P. falciparum* where the two species are co-endemic.

Maitland and colleagues have suggested that the earlier age peak for *P. vivax* disease may protect against the later-acquired *P. falciparum* through species-transcending immunity [12]. Studies have shown that symptoms of *P. vivax* or *P. falciparum* infection are, indeed, significantly reduced by recent previous *P. vivax* infection (but not *P. falciparum* infection) [13]. In contrast, the two new studies in *PLoS Medicine* report that mixed species infections had worse outcomes than infections of either species alone [1,2]. If previous vivax infection does protect against severe *P. falciparum* infection, further investigations are needed so that policies for *P. vivax* control can balance reduction in severe vivax with possible loss of vivax-associated protection against severe *P. falciparum* infection.

Malaria Severity Depends on Context

The findings of the two new studies [1,2] should be considered from a wider biological and historical perspective, which shows that malarial disease severity is highly context dependent. For example, from the 16th through the 19th centuries in England, mortality rates associated with “marsh agues”—probably due largely to vivax malaria—gradually fell from high to negligible levels. This fall occurred either because of attenuation of *P. vivax* infection through adaptation of parasite and/or host, or through environmental change, such as reduced exposure to other diseases or improved nutrition [14]. Indeed, host under-nutrition and co-infections, including HIV, helminth, and acute bacterial or viral infections, can all influence the outcomes in malaria [3]. Access to effective diagnostic tools to identify mixed infections in particular [4]. Some “severe vivax” cases may actually have been mixed infections.

Severe Vivax Malaria

Despite these limitations, a striking feature of the two studies is the overall comparable incidence of severe disease in *P. vivax* and *P. falciparum* infections in each setting. There were differences in the prevalence of the components of severe disease in the two locations and a notable disparity in the overall rates of severe disease. This, in Timika, anaemia defined severe malaria more often than in Wosera, where anaemia was especially infrequent in severe vivax. This difference may be attributable to the fact that in Timika, both *P. vivax* and *P. falciparum* were commonly resistant to chloroquine, the first-line malaria treatment (with sulfadoxine–pyrimethamine in the case of *P. falciparum*), for much of the study period. Because persistent blood infections with malaria are likely to increase anaemia, drug treatment failure could have contributed to the high anaemia rates in Timika. In Wosera, where chloroquine resistance is common in *P. falciparum* but rare in *P. vivax*, severe anaemia defined 40% of severe falciparum cases, but only 20% of severe vivax cases. Thus the Wosera data are also consistent with parasite drug resistance as a factor in anaemia. If these conjectures are correct, the recent adoption of dihydroartemisinin–piperaquine treatment in Papua [5] may lead to a significant decrease in severe malarial anaemia.

Other factors, such as host genetics, could also have influenced the differences in severe disease manifestation between study sites. It has been shown, for example, that children in Papua New Guinea with the red cell genetic polymorphism “South East Asian ovalocytosis”, a trait common in this population, are almost completely protected from cerebral malaria [6]. In Timika, indigenous Papuans were much more likely to be severely anaemic than were immigrants. Host genetics may contribute to the high anaemia rates reported in the Timika study.

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**Box 1. Crucial Tools for *P. vivax* Control**

- **Effective first-line treatment.** Artemisinin-based combination therapies are generally effective, but longer-acting combinations may additionally prevent early relapses.
- **Highly sensitive rapid diagnostic tests.** Present tests are inadequately sensitive at low parasitaemia, which is common in *P. vivax*.
- **Preventive therapy.** The role of intermittent preventive treatment in pregnancy or childhood against vivax is unknown. Small studies suggest that insecticide-treated bed nets are effective against *P. vivax*.
- **Safe drugs for elimination of liver stages.** G6PD deficiency, selected for by malaria, can result in fatal haemolysis from current agents.
- **Vaccination.** New vaccines are entering human trials. If efficacious, their deployment will require major planning efforts.

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**Five Key Papers in the Field**

**Grimberg et al., 2007 [19]**

The investigators show that antibodies directed against “region two” of PvDBP inhibit merozoite invasion, suggesting that vaccines targeted towards this region could reduce blood stage infection.

**Barcus et al., 2007 [7]**

Along with the two new papers in this issue of *PLoS Medicine* [1,2], Barcus and colleagues’ study contributes to our understanding of the importance of *P. vivax* as a cause of severe clinical disease.

**Panichkul et al., 2007 [21]**

This paper represents a significant advance in the difficult process of developing robust in vitro culture systems for *P. vivax*.

**Ratcliff et al., 2007 [5]**

Both treatments cured falciparum and vivax malaria with high efficacy, but dihydroartemisinin–piperaquine was much better than artemether–lumefantrine at preventing re-infections with *P. falciparum* and relapses of *P. vivax* during a six-week follow-up.

**Singh et al., 2006 [18]**

This paper shows how the Duffy binding protein interacts with its ligand, which is also relevant to understanding structure and interactions of other important adhesive proteins of malaria parasites.
to antimalarial drugs and presence of parasite drug resistance are clearly also relevant to the clinical outcome. 

P. vivax infection is characterised by relapse in which dormant liver stages awaken, initiating new bouts of blood infection. Repeated malarial blood infections, from whatever source, have debilitating consequences including cachexia, spontaneous abortions, male infertility, developmental arrest, and impaired mental function [15]. All of these debilitating clinical features have been present in populations where P. vivax is known, or presumed, to have been the main prevalent malaria. However, these manifestations are also context dependent—they are influenced by circumstances such as the level of endemicity, existence of co-infections, access to treatment, and presence of parasite resistance. It is interesting that the present reports of severe vivax malaria come from New Guinea, where drug-resistant P. vivax was first reported. This drug resistance itself could be a driver of severity together with the particularly high regional malaria transmission force. Were severe vivax to be found more widely, it would have significant implications for control of the infection, especially as P. vivax invariably increases relative to P. falciparum under effective transmission reduction [16].

The Way Forward for Vivax Malaria Control

With calls for increased efforts to control malaria internationally, it will be important to ensure that P. vivax receives appropriate attention. We still lack reliable estimates of its global burden, and are only now starting to appreciate certain aspects of disease presentation of P. vivax malarial infection. The burden and severity of vivax in different settings requires further study. With the availability of the P. vivax genome (GenBank accession no. AAKM00000000), it will be possible to compare isolates associated with severe or uncomplicated disease. However, connecting genetic differences with pathogenic potential may not be straightforward [17].

Better disease control (see Box 1) might include preventive strategies (vaccines, insecticide-treated bed nets, and intermittent preventive treatment), more effective curative treatment (finding the most suitable alternative to chloroquine), and better relapse prevention (long-acting drugs such as dihydroartemisinin-piperazine decrease early relapse compared to other artemisinin-based combination therapies [5]). Elimination of dormant parasites in the liver (hypnozoites) is especially difficult because available drugs can cause severe haemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. A simple point-of-care assay for G6PD deficiency, or new, safer drugs that target liver stage parasites, would be invaluable tools for eradication of hypnozoites.

Vaccines against P. vivax are in development. One target is the P. vivax Duffy binding protein (PvDBP), which mediates merozoite invasion of erythrocytes [18, 19]; human vaccine studies using this target are likely to begin this year. Another target is the P. vivax gamete surface protein Pvs25, a candidate for a transmission-blocking vaccine. Indeed, this vaccine candidate is already in Phase I human trials [20]. Should either candidate progress to large-scale trials, it will be critical to examine impact on both P. vivax infection (including, potentially, increased chronicity of infection and anaemia following PvDBP vaccination) and P. falciparum infection. While New Guinea is an ideal site in which to evaluate such vaccines, evaluation must also be done in low-transmission areas where most P. vivax infections are symptomatic, and where diminished symptomatology could dangerously postpone treatment. The two reports by Price et al. and Genton et al. provide information about disease burden critical to improved decision making for the public health management of P. vivax malaria [1, 2].

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References