

Research in Translation

Severe Vivax Malaria: Newly Recognised or Rediscovered?

Stephen J. Rogerson*, Richard Carter

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 *P. 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 mild. However, two studies published in this issue of *PLoS Medicine* challenge this dogma.

The Two New Studies

Ric Price and colleagues, in a prospective study based in Timika, southern Papua in Indonesia [1], and Blaise Genton and colleagues, in a prospective study in the Wosera region of Papua New Guinea [2], report similar rates and outcomes of severe malaria due to *P. vivax* or *P. falciparum*. The two studies had different settings, and the cultural and ethnic characteristics of the patient populations were also different. Price and colleagues collected data from all patients attending the outpatient and inpatient departments of the only hospital in the region, using systematic data forms and computerised hospital records. In contrast, Genton and colleagues investigated patients presenting at two rural health facilities.

In both settings, clinical and severe disease was most common in young children, with *P. vivax* cases peaking at an earlier age than those of *P. falciparum*. In Timika, in children under five years old, around 30% of cases of either *P. falciparum* or *P. vivax* were classed as severe, and around 80% of such cases were accompanied by severe anaemia (haemoglobin less than 5 g/dl). The remainder presented with respiratory distress, impaired

Research in Translation discusses health interventions in the context of translation from basic to clinical research, or from clinical evidence to practice.

Linked Research Articles

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

Genton B, D'Acremont V, Rare L, Baea K, Reeder JC, et al. (2008) *Plasmodium vivax* and mixed infections are associated with severe malaria in children: A prospective cohort study from Papua New Guinea. *PLoS Med* 5(6): e127. doi:10.1371/journal.pmed.0050127

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

Tjitra E, Anstey NM, Sugiarto P, Warikar N, Kenangalem E, et al. (2008) Multidrug-resistant *Plasmodium vivax* associated with severe and fatal malaria: A prospective study in Papua, Indonesia. *PLoS Med* 5(6): e128. doi:10.1371/journal.pmed.0050128

Ric Price and colleagues present data from southern Papua, Indonesia, suggesting that malaria resulting from infection with *Plasmodium vivax* is associated with substantial morbidity and mortality.

consciousness (i.e., cerebral malaria), or overlapping syndromes. In the Wosera, in children under five years attending the health centre, around 9% of vivax and 12% of falciparum infections were classified as severe malaria. However, respiratory distress was defined less stringently in the Wosera (more than 40 breaths/minute from two to 60 months) than in Timika (more than 50 breaths/minute in this age group). When cough and diarrhoea (which are poorly specific for malaria) were used as exclusions in the Wosera study, severe malaria rates in children under five years fell to 7% and 4% of *P. falciparum* and *P. vivax* infections, respectively. In the Wosera, anaemia occurred in about 20% and 40% of severe cases of vivax and falciparum, respectively, while respiratory distress occurred in 60%

and 40% of severe cases of vivax and falciparum, respectively. Neurologic symptoms were present in 25% of severe cases of either species.

The cases of cerebral malaria due to *P. vivax* reported in both studies, occurring in all age groups, are intriguing, because this malaria complication has rarely been reported previously in association with *P. vivax* infection. In *P. falciparum*, cerebral malaria is primarily attributed to sequestration of infected erythrocytes in cerebral vessels. As *P. vivax* does not sequester, coma must arise by other means—perhaps of systemic metabolic origin—in vivax malaria. This aetiology may also underlie some cerebral malaria presentations in children.

Both studies, inevitably, have limitations. First, co-morbidities, including concomitant bacterial or viral infections, which could have decreased the malaria-attributable fraction of disease [3], were not actively investigated. Second, microscopy was used for parasite detection and speciation, which routinely leads to

Funding: The authors received no specific funding for this article.

Competing Interests: The authors have declared that no competing interests exist.

Citation: Rogerson SJ, Carter R (2008) Severe vivax malaria: Newly recognised or rediscovered? *PLoS Med* 5(6): e136. doi:10.1371/journal.pmed.0050136

Copyright: © 2008 Rogerson and Carter. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

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

Stephen J. Rogerson is in the Department of Medicine, University of Melbourne, Royal Melbourne Hospital, Parkville, Victoria, Australia. Richard Carter is at the Institute of Immunology and Infection Research, School of Biological Sciences, The University of Edinburgh, Ashworth Laboratories, Edinburgh, United Kingdom.

* To whom correspondence should be addressed. E-mail: sroger@unimelb.edu.au

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 decrease disease.
- **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.

marked underestimation of 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. Thus, 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. Might host genetics have contributed 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 undernutrition and co-infections, including HIV, helminth, and acute bacterial or viral infections, can all influence the outcomes in malaria [3]. Access

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.

Panichakul 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 awoken, 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–piperaquine 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]. ■

Acknowledgments

We thank Dr. Kamini Mendis for discussions.

References

- Tjitra E, Anstey NM, Sugiarto P, Warikar N, Kenangalem E, et al. (2008) Multidrug-resistant *Plasmodium vivax* associated with severe and fatal malaria: A prospective study in Papua, Indonesia. *PLoS Med* 5: e128. doi:10.1371/journal.pmed.0050128
- Genton B, D'Acremont V, Rare L, Baea K, Reeder JC, et al. (2008) *Plasmodium vivax* and mixed infections are associated with severe malaria in children: A prospective cohort study

- from Papua New Guinea. *PLoS Med* 5: e127. doi:10.1371/journal.pmed.0050127
- Bejon P, Berkley JA, Mwangi T, Ogada E, Mwangi I, et al. (2007) Defining childhood severe falciparum malaria for intervention studies. *PLoS Med* 4: e251. doi:10.1371/journal.pmed.0040251
- Mayxay M, Pukrittayakamee S, Newton PN, White NJ (2004) Mixed-species malaria infections in humans. *Trends Parasitol* 20: 233-240.
- Ratcliff A, Siswanto H, Kenangalem E, Maristela R, Wuwung RM, et al. (2007) Two fixed-dose artemisinin combinations for drug-resistant falciparum and vivax malaria in Papua, Indonesia: An open-label randomised comparison. *Lancet* 369: 757-765.
- Genton B, al-Yaman F, Mgone CS, Alexander N, Panii MM, et al. (1995) Ovalocytosis and cerebral malaria. *Nature* 378: 564-565.
- Barcus MJ, Basri H, Picarima H, Manyakori C, Sekartuti, et al. (2007) Demographic risk factors for severe and fatal vivax and falciparum malaria among hospital admissions in northeastern Indonesian Papua. *Am J Trop Med Hyg* 77: 984-991.
- Allen SJ, O'Donnell A, Alexander ND, Clegg JB (1996) Severe malaria in children in Papua New Guinea. *Q J Med* 89: 779-788.
- Marsh K, Forster D, Waruiru C, Mwangi I, Winstanley M, et al. (1995) Indicators of life-threatening malaria in African children. *N Engl J Med* 332: 1399-1404.
- Issifou S, Kendjo E, Missinou MA, Matsiegui PB, Dzeing-Ella A, et al. (2007) Differences in presentation of severe malaria in urban and rural Gabon. *Am J Trop Med Hyg* 77: 1015-1019.
- Reyburn H, Mbatia R, Drakeley C, Bruce J, Carneiro I, et al. (2005) Association of transmission intensity and age with clinical manifestations and case fatality of severe *Plasmodium falciparum* malaria. *JAMA* 293: 1461-1470.
- Maitland K, Williams TN, Newbold CI (1997) *Plasmodium vivax* and *P. falciparum*: Biological interactions and the possibility of cross-species immunity. *Parasitol Today* 13: 227-231.
- Gunawardena DM, Carter R, Mendis KN (1994) Patterns of acquired anti-malarial immunity in Sri Lanka. *Mem Inst Oswaldo Cruz* 89: 61-63.
- Dobson MJ (1994) Malaria in England: A geographical and historical perspective. *Parassitologia* 36: 35-60.
- Sinton JA (1935-6) What malaria costs India, nationally, socially and economically. *Rec Mal Survey India* 5: 223-264, 413-489; 6: 292-169.
- Mendis K, Sina BJ, Marchesini P, Carter R (2001) The neglected burden of *Plasmodium vivax* malaria. *Am J Trop Med Hyg* 64: 97-106.
- Feng X, Carlton JM, Joy DA, Mu J, Furuya T, et al. (2003) Single-nucleotide polymorphisms and genome diversity in *Plasmodium vivax*. *Proc Natl Acad Sci U S A* 100: 8502-8507.
- Singh SK, Hora R, Belrhali H, Chitnis CE, Sharma A (2006) Structural basis for Duffy recognition by the malaria parasite Duffy-binding-like domain. *Nature* 439: 741-744.
- Grimberg BT, Udomsangpet R, Xainli J, McHenry A, Panichakul T, et al. (2007) *Plasmodium vivax* invasion of human erythrocytes inhibited by antibodies directed against the Duffy binding protein. *PLoS Med* 4: e337. doi:10.1371/journal.pmed.0040337
- Malkin EM, Durbin AP, Diemert DJ, Sattabongkot J, Wu Y, et al. (2005) Phase I vaccine trial of Pvs25H: A transmission blocking vaccine for *Plasmodium vivax* malaria. *Vaccine* 23: 3131-3138.
- Panichakul T, Sattabongkot J, Chotivanich K, Sirichaisinthop J, Cui L, et al. (2007) Production of erythropoietic cells in vitro for continuous culture of *Plasmodium vivax*. *Int J Parasitol* 37: 1551-1557.