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HOLOENDEMIC SETTING OF  
*PLASMODIUM FALCIPARUM* AND *P. VIVAX*  
MALARIA

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## EDITORIAL ACQUIRED IMMUNITY IN A HOLOENDEMIC SETTING OF *PLASMODIUM FALCIPARUM* AND *P. VIVAX* MALARIA

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Most of what we presume to understand of naturally acquired immunity to *Plasmodium falciparum* malaria comes from studies in sub-Saharan Africa. The virtual absence of *P. vivax* malaria from most of that region leaves three important questions not addressed: 1) What is naturally acquired immunity to *P. vivax* malaria; 2) do the mechanisms of natural immunity to *P. falciparum* and *P. vivax* malaria differ, and 3) what influence does one species exert on acquisition of immunity to the other? Naturally acquired immunity requires repeated and frequent exposure to infection, and few places offer sufficient exposure to both *P. falciparum* and *P. vivax* to allow examination of these questions.

The certainty of naturally acquired immunity to *P. vivax* malaria derives almost entirely from studies of neurosyphilis patients treated by repeated exposure to induced infections by *P. vivax*. As with *P. falciparum*, a half dozen or so exposures over a relatively brief period resulted in far lower density parasitemia and no fever. In terms of understanding naturally acquired immunity, the neurosyphilis work has two important sources of sample bias: 1) all subjects were adults, and 2) homologous strains of parasites were usually used. These biases, combined with the relatively rapid onset of immunity in the clinic, ironically share some responsibility for the long-held belief that immunity acquired by natural infections required more than a dozen or so years of chronic, heavy exposure. The rapid onset of immunity in neurosyphilis patients was attributed to the use of homologous strains, and the seemingly slow onset of immunity in exposed populations was attributed to the heterologous nature of wild strains.

This framework allowed elegant theories of susceptibility driven by antigenic polymorphism and variability, but it also failed to answer critical questions. Do children differ inherently from adults in their immune management of repeated infections? Do children enjoy rapid onset of clinical immunity when challenged with homologous strains? Is onset of clinical immunity in adults rapid with challenge by heterologous strains? These gaps in understanding could only be addressed with studies in natural settings. In this issue of the journal, Michon and others<sup>1</sup> follow a cohort of school age children in holoendemic Papua New Guinea having a remarkably high and largely equal number of exposures to *P. falciparum* and *P. vivax*. Their work provides a rare glimpse at naturally acquired immunity to *P. vivax* malaria and allows an insightful contrasting look at the same in *P. falciparum* malaria.

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Their cohort of children was at equivalent risk of acquiring either *P. vivax* or *P. falciparum* infections from the local vector populations but 21 times more likely to develop an overt clinical response to *P. falciparum* than to *P. vivax*. The ability to regulate parasite densities of *P. vivax* was also evident after nine years of age and there was no evidence of *P. falciparum* density regulation throughout the school age period. The occurrence of a more complete clinical and anti-parasitic immunity earlier in life for *P. vivax* compared with *P. falciparum* despite comparable levels of exposure suggests different mechanisms of acquired immunity for the two most common malaria parasites. Whether these are host-response, individual parasite, or combined exposure related remains uncertain but merit more detailed epidemiologic investigation. These observations buttress similar conclusions from other studies, and emphasize the apparently strict homology of immunity within these species and perhaps the distinct immune mechanisms at work between species.

Collins and Jeffery described essentially similar observations in neurosyphilis patients<sup>2</sup>, and corroboration from natural settings gives weight to the experimental findings. The results reported by Michon and others derive from an elegant field epidemiology study of infection and disease incidence. These detailed cohort studies provide us with a wealth of information under conditions of natural exposure and provide not only insights into the immunology of infection and disease but also a reliable measure of public health burdens. These study designs should be encouraged across a wider range of transmission settings and dominant vector species ecologies to improve the externality of single observations.

The spatial congruence of major public health infections has led to a renewed interest in the epidemiology and control of polyparasitic disease, including interactions and public health outcomes associated with *P. falciparum* malaria and human immunodeficiency virus<sup>3,4</sup> or *P. falciparum* malaria and soil-transmitted helminths.<sup>5,6</sup> Perhaps one of the largest and largely ignored coincidental distributions of different parasites is the overlap between *P. vivax* and *P. falciparum*. It has recently been estimated that 1.98 billion people are at possible risk of both parasites worldwide.<sup>7</sup> Now would be a good time to increase efforts to understand the epidemiology of two of the most significant parasite species sharing the widest global reach. Paradoxically, the neglected epidemiology and immunology of *P. vivax* malaria may be effectively leveraged to more fully understand acquired immunity to *P. falciparum* malaria.

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