The validated method was successfully applied to determine the plasma concentrations of ART, DHA, LUM and DBL in pregnant and non-pregnant women volunteers in a multiple-dose pharmacokinetics study over the course of 336 hours.

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MODELING HOST-PARASITE INTERACTIONS IN MALARIA BLOOD-STAGE INFECTIONS IN RHESUS MACAQUES

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Malaria is globally the most deadly parasitic disease in humans, and the long-time coexistence with malaria has left indelible marks in the human genome that are the causes of a variety of genetic disorders. Anemia is the most common and severe complication of malaria, yet the root causes and mechanisms involved in malarial anemia are unclear and very difficult to study in humans. Non-human primate model systems enable the study and quantification of underlying, causative factors of malarial anemia, and particularly the onset of severe anemia. A discrete recursive model was developed to simulate host-parasite interactions during the blood stage infection; it accounts for reticulocytes, red blood cells (RBCs), and infected RBCs. The parameters of this mechanistic model were optimized against the readouts of individual macaque data, which had been obtained in the course of *Plasmodium coatneyi* and *P. cynomolgi* infections of cohorts of malaria-naïve rhesus macaques (*Macaca mulatta*). The model allowed detailed estimations of the levels of erythropoietic output, reticulocyte lifespan, RBC removal, and the immune response against the parasite in each macaque. The results showed that rhesus macaques have a response to a *P. cynomolgi* infection that is difficult to understand: As expected, the infection resulted in anemia, yet 60% of the RBCs were lost by bystander effect a mechanism other than parasite invasion. To compensate for the severe anemia, the host released younger reticulocytes and increased the erythropoietic output. These responses, however, appeared to be poorly coordinated, as the release of younger reticulocytes occurred too early, while anemia had not yet set in, thereby probably aiding the parasite more than the host. Increased production of RBCs was only detected after treatment that lowered the parasitemia. The model also showed that, similarly to humans, reticulocytes in rhesus macaques circulate for about 24h before becoming mature RBCs. Anemia, as a sequela of malaria, was due in 60% to bystander destruction of RBCs, and by an inability of the host to up-regulate erythropoiesis before suppression of parasitemia.

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GLOBAL ECONOMIC COSTS DUE TO *PLASMODIUM VIVAX* MALARIA TREATMENT AND THE COST-BENEFIT OF RADICAL CURE

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The global cost burden related to the treatment of vivax malaria has not been assessed. Here we estimated the current global economic cost of illness to healthcare providers and patient households and to explore the potential cost-benefit of implementing radical cure following a normal G6PD test result. Estimates of the cost of vivax malaria treatment for healthcare providers and patient households were collated from a literature review and primary costing studies, and combined with case estimates generated by the Malaria Atlas Project. A cost-benefit analysis of implementing effective global radical cure compared the cost of G6PD screening and supervised radical cure with the cost savings from the prevention of relapses. It was assumed that when adhered to, the 14-day primaquine regimen was 85% effective and required 3.5 healthcare worker days to supervise daily therapy (valued at one gross domestic product per capita per day). The estimate of the global cost of *P. vivax* was US$330 million (range US$205-459 million). Adopting a policy of screening for G6PD deficiency and delivery of highly effective radical cure was projected to save US$45 million per year from the societal perspective. Household costs decreased by US$124 million; however, provider costs increased by US$80 million attributable primarily to the inclusion of supervised primaquine therapy. The global societal costs of vivax malaria are substantial, but can be reduced through the use of effective radical cure following screening for G6PD deficiency. Novel, less costly interventions for ensuring adherence to primaquine regimens for effective radical cure are needed to reduce healthcare provider costs and provide a pathway to malaria elimination.

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MULTIPLICITY OF INFECTION - HOW TO ESTIMATE IT AND HOW TO DESIGN YOUR STUDY

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Multiplicity of infection (MOI), i.e., the number of super-infections, is a potent measure of transmission intensities in malaria, which can be incorporated into metrics for monitoring disease-control interventions. It can be readily estimated from molecular data gained from parasite-positive blood samples using different methods, some of which use ad hoc approximations while others are based on statistical models. While the focus has been on applications, the statistical properties of such methods and their impact on study designs have received less attention. Targeted to theoreticians and applied researchers, we present the statistical properties of a maximum-likelihood (ML) method to estimate MOI along with allele frequencies at molecular markers and compare them with some ad hoc methods. Particularly, we report on the asymptotic and finite-sample properties. While the ML estimate has the typical desirable asymptotic properties (asymptotic unbiasedness, consistency, efficiency) and adequate finite-sample properties, alternative ad-hoc methods might be severely biased. Particularly, ad hoc methods are not asymptotically unbiased, leading to misinferences even in large samples. Additionally, the ML estimate is relatively robust against model violations, as confirmed by a simulation study. Furthermore, the method is easy to compute and available as an R script. Moreover, it is possible to adapt the statistical model for study design purposes in order to ensure precision and accuracy goals when estimation MOI and allele frequencies. We apply illustrate the methods on a data set from Venezuela and exemplify sample-design issues.

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CAUSAL DISCOVERY WITH KERNEL INDEPENDENCE TESTS FOR UNDERSTANDING AND MODELLING SEASONALITY OF MALARIA TRANSMISSION

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Seasonality in malaria transmission is observed widely around the world and varies greatly between areas, even varying from village to village in the same region and between different years. Many environmental factors have been identified as possible drivers of seasonality, including temperature, rainfall and vegetation. Many studies have also considered these covariates with various time-lags. Other data summaries may also be considered, such as mean monthly rainfall or total rainfall over a set time interval, as well as non-environmental factors, resulting in a large number of candidate drivers of seasonality. Due to the many possible covariates and highly variable nature of malaria seasonality around the world, standard regularisation techniques in machine learning may have trouble correctly identifying important covariates. We performed causal inference