Levels of naturally acquired IgG antibodies to the apical membrane protein 1 (AMA1) and risk of subsequent *Plasmodium vivax* infection in Amazonians: a time-to-recurrence study

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Background. Antibodies to the apical membrane protein 1 (AMA1) of *Plasmodium vivax* are often detected in malaria-exposed individuals, but evidence for protective antibody responses has only recently emerged. Importantly, a recombinant human monoclonal antibody has shown to block entry of *P. vivax* merozoites into reticulocytes and inhibit sporozoite invasion of hepatocytes in vitro.

Objective. Test whether naturally acquired antibodies to AMA1 circulating during an acute *P. vivax* infection can predict the risk of subsequent clinical vivax malaria.

Methods. Pre-treatment plasma samples from patients in an open-label randomized trial of chloroquine (CQ) alone or CQ-primaquine (PQ) for uncomplicated *Plasmodium vivax* malaria were tested for IgG antibodies by indirect ELISA using the AMA1 ectodomain (residues 43–487) expressed in *Pichia pastoris*. The primary endpoint was time to first microscopy-confirmed recurrent vivax malaria between days 29 and 180 post-treatment. Cox proportional hazards models compared hazard ratios across terciles of anti-AMA1 antibody levels, stratifying for sex and adjusting for age, treatment arm, and CYP2D6 genotype.

Results. Anti-AMA1 IgG antibodies were detected in 99.4% (171 of 172) participants. All remained free of microscopically detected *P. vivax* infection until day 28, but 51 (29.6%) experienced at least one *P. vivax* recurrence between days 29 and 180 of follow-up. The time to the first clinical vivax malaria episode was delayed among high responders compared to low responders to AMA1 (third vs. first tercile); HR = 0.62 (95% CI, 0.28 to 1.35); but such a difference did not reach statistical significance (P = 0.23).

Conclusion. High levels of anti-AMA1 IgG antibodies during an acute infection do not predict a significantly lower risk of *P. vivax* recurrence over the next 180 days. We are currently testing whether our study participants have anti-AMA1 antibodies that compete with protective human monoclonal antibodies for the same or nearby epitopes.

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