Malaria infection induces oxidative stress in the host cells. Antioxidant enzymes such as glutathione S-transferases (GSTs) are responsible for fighting reactive oxygen species and reduction of oxidative stress. Common GST polymorphisms have been associated with susceptibility to different diseases whose pathologies involve oxidative stress. In this study, we tested the hypothesis that GST polymorphisms that lead to reduced or lack of enzyme activity are associated with severe Plasmodium falciparum malarial anemia. We studied the genotypic distribution of GSTM1, GSTT1, and GSTP1 polymorphisms between mild malaria (N = 107) and severe malarial anemia (N = 50) in Tanzanian children. We did not find a significant relationship with the GSTT1 polymorphism. GSTM1-null was higher in the severe malaria anemia group but the difference was not significant (P = 0.08). However, a significant association of GSTP1 I105V genotype with severe malarial anemia was discovered (26.0% against 10.3% mild malaria, P = 0.004). We concluded that GSTP1 and possibly GSTM1 may protect against severe falciparum malaria in children.
Germany), polymerase chain reaction (PCR) was performed using native, Taq polymerase (invitrogen) and all primers were purchased from Biologio, Nijmegen, The Netherlands. Primers for GSTT1, GSTM1, and GSTP1 were designed according to Pemble and others, Bröckmoller and others, and Watson and others, respectively. The PCR conditions for GSTM1, GSTT1, and GSTP1 were followed as previously described. Samples that gave negative results for GSTT1 and T1 were measured again with β-globin as a control.

The results of the polymorphism analysis in mild and severe malaria are depicted in Table 2. For GSTM1 there was a higher prevalence of GSTM1-null genotype in the severe group (40%) than in the mild group (26%), although not statistically significant (P = 0.08). The observed distributions in mild malaria are comparable to the reported distribution of GSTM1-null in African population (22–39%). In Caucasian population, however, the GSTM1-null frequency is higher (around 50%) than in the African population. In our previous study with 138 children from Cameroon, we found a statistically significant difference for the GSTM1-null frequency: 32% and 58% in uncomplicated malaria and severe malaria, respectively.

The prevalence of homozygous GSTP1 I105V in the severe malaria group (26.0%) was significantly higher than in the mild group (10.3%). This indicates for the first time an association of the GSTP1 I105V genotype with severe malaria. There is evidence that the GSTP1 I105V polymorphism may have a substrate-dependent effect on the enzyme activity. The general distribution of the homozygous GSTP1 I105V genotype in the mild malaria group is comparable to previous studies in a Brazilian population of African descent (8.3%) and Caucasians (11.3%). In our previous study with Cameroonian children, we found in uncomplicated malaria (21%) and severe malaria (26%) frequencies that are comparable to what we now observe in severe malaria (26%).

When a combined analysis of GSTM1 and GSTP1 was performed, the presence of wild-type condition on one or both of the two genes was 64.0% and 83.2% for the severe and mild malaria groups, respectively, and for the presence of mutations on both enzymes (hetero- or homozygous mutant) was 36.0% and 16.8% for the severe and mild malaria groups, respectively (P = 0.007).

The prevalence of GSTT1-null was comparable in both groups (48% and 54%). In the Cameroonian study we also observed no differences; although the frequencies were lower (21% and 29%).

This study has shown association of GSTP1 I105V, and a trend but not significant association of GSTM1, with severe malaria anemia. GSTP1 and GSTM1 are expressed in all blood cells with higher expression in lymphoid than erythroid cell types, whereas GSTT1 and GSTA are expressed in higher levels in erythrocytes than in lymphoid cells. In this study, we did not investigate on GSTA and we did not detect an association of GSTT1 with malaria, which is consistent with our previous observation. It is not clear how GST polymorphisms can affect the malaria infection outcome. The GSH is important for parasite growth and in vitro studies have documented detoxification of heme via a GSH-utilizing pathway, that can be inhibited by chloroquine and amodiaquine. Furthermore, drugs known to reduce cellular GSH were shown to potentiate the action of chloroquine in drug-resistant rodent malaria.

Glutathione S-transferase (GST) polymorphisms can change the enzyme activity, which can lead to reduced detoxification of the host cell or increased availability of host GSH that might be used by the parasite. In both cases the malaria pathology could be accelerated. It is also likely that the impact of GSTs is not direct on erythrocytes but on other cells that are involved in the immune response mechanisms and that severe malarial anemia as an outcome can partly be attributed to such responses. Therefore, further studies including in vitro cellular studies to assess malarial outcomes for specific GST polymorphism genotypes are important.

In conclusion, GSTP1 and possibly GSTM1 may have protective effects against severe falciparum malaria in children. The contribution of specific GST polymorphisms to severe disease may differ between populations or geographic areas. These findings do not undermine the importance of oxidative stress in malaria clearance, but rather provide a broader perspective on the impact of oxidative stress on both the host and parasite cells.

Received November 27, 2008. Accepted for publication April 18, 2009.

Financial support: Reginald A. Kavishe is supported by NWO-WOTRO (WIZ93-465) through PRIOR.
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Authors’ addresses: Reginald A. Kavishe, Frans G. M. Russel, and Jan B. Koenderink, Department of Pharmacology and Toxicology 149, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmegen, The Netherlands. Teun Bousema and Robert W. Sauerwein, Department of Medical Microbiology 268, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmegen, The Netherlands. Seif A. Shekalaghe and Frank W. Mosha, Kilimanjaro Christian Medical College of Tumaini University, PO Box 2240, Moshi, Tanzania. André J. A. M. van der Ven, Department of Internal Medicine 463, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmegen, The Netherlands.

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