Patterns of inflammatory responses and parasite tolerance vary with malaria transmission intensity

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In individuals living in malaria-endemic regions, parasitaemia thresholds for the onset of clinical symptoms vary with transmission intensity. The mechanisms that mediate this relationship are however, unclear. Since inflammatory responses to parasite infection contribute to the clinical manifestation of malaria, we investigated inflammatory cytokine responses in children with malaria from areas of different transmission intensities (ranging from low to high). Blood samples were obtained from children confirmed with malaria at community hospitals in three areas with differing transmission intensities. Cytokine levels were assessed using the Luminex®-based magnetic bead array system, and levels were compared across sites using appropriate statistical tests. The relative contributions of age, gender, parasitaemia and transmission intensity on cytokine levels were investigated using multivariate regression analysis. We found that parasite density increased with increasing transmission intensity in children presenting to hospital with symptomatic malaria, indicating that the parasitaemia threshold for clinical malaria increases with increasing transmission intensity. Furthermore, levels of pro-inflammatory cytokines, including tumour necrosis factor alpha (TNF-α), interferon-γ (IFN- γ), interleukin (IL)-1β, IL-2, IL-6, IL-8, and IL-12, decreased with increasing transmission intensity, and correlated significantly with parasitaemia levels in the low transmission area but not in high transmission areas. Similarly, levels of anti-inflammatory cytokines, including IL-4, IL-7, IL-10 and IL-13, decreased with increasing transmission intensity, with IL-10 showing strong correlation with parasitaemia levels in the low transmission area. Multiple linear regression analyses revealed that transmission intensity was a stronger predictor of cytokine levels than age, gender and parasitaemia. Taken together, the data demonstrate a strong relationship between the prevailing transmission intensity, parasitaemia levels and the magnitude of inflammatory responses induced during clinical malaria.