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Decreasing Efficacy of Antimalarial Combination Therapy in Uganda is Explained by Decreasing Host Immunity Rather than Increasing Drug Resistance.

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BACKGROUND: Improved control efforts are reducing the burden of malaria in Africa but may result in decreased antimalarial immunity.

METHODS: A cohort of 129 children aged 1-10 years in Kampala, Uganda, were treated with amodiaquine plus sulfadoxine-pyrimethamine for 396 episodes of uncomplicated malaria over a 29-month period as part of a longitudinal clinical trial.

RESULTS: The risk of treatment failure increased over the course of the study from 5% to 21% (hazard ratio [HR], 2.4 per year [95% confidence interval {CI}, 1.3-4.3]). Parasite genetic polymorphisms were associated with an increased risk of failure, but their prevalence did not change over time. Three markers of antimalarial immunity were associated with a decreased risk of treatment failure: increased age (HR, 0.5 per 5-year increase [95% CI, 0.2-1.2]), living in an area of higher malaria incidence (HR, 0.26 [95% CI, 0.11-0.64]), and recent asymptomatic parasitemia (HR, 0.06 [95% CI, 0.01-0.36]). In multivariate analysis, adjustment for recent asymptomatic parasitemia, but not parasite polymorphisms, removed the association between calendar time and the risk of treatment failure (HR, 1.5 per year [95% CI, 0.7-3.4]), suggesting that worsening treatment efficacy was best explained by decreasing host immunity.

CONCLUSION: Declining immunity in our study population appeared to be the primary factor underlying decreased efficacy of amodiaquine plus sulfadoxine-pyrimethamine. With improved malaria-control efforts, decreasing immunity may unmask resistance to partially efficacious drugs.

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