Low-dose treatment may block malaria transmission

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Lower doses of the antimalarial drug primaquine are as effective as higher doses in reducing malaria transmission, according to a study published today in *Lancet Infectious Diseases* by London School of Hygiene & Tropical Medicine researchers.

Primaquine is one of the few antimalarial drugs that targets the transmission stages of the malaria parasite, the gametocytes, and is therefore considered to be an important tool for malaria elimination.

However, standard doses of the drug cause reduced blood count in individuals with a deficiency in glucose-6-phosphate dehydrogenase (G6PD) enzyme. This red blood cell disorder is common in malaria endemic areas, and has therefore limited the use of primaquine in malaria programmes, and prompted the World Health Organization (WHO) to advise a reduction in dosage from 0.75 mg/kg to 0.25mg/kg. But until now, the efficacy of lower doses of primaquine had not been formally evaluated.

The study, carried out in Jinja, Uganda, treated G6PD-normal children with a conventional anti-malarial drug either on its own or with one of three different doses of primaquine. The subsequent carriage of malaria gametocytes was monitored for two weeks and safety outcomes were monitored for four weeks. Results showed that a dose of 0.4 mg/kg, approximately half of the previously recommended dose (0.75 mg/kg), was as effective at reducing the transmission potential of individuals with malaria.

These results establish that low dose primaquine is still effective and safe in a G6PD-normal population, and paves the way for using low-dose primaquine as a component of strategies to reduce malaria transmission and to stop the spread of drug-resistant malaria parasites.

The next step is to include the current WHO-recommended 0.25 mg/kg dose of primaquine in efficacy studies, and to test the safety of low dose primaquine in G6PD-deficient individuals.

Lead author Dr Chi Eziefula, Wellcome Trust clinical research fellow, said: "Until now, the use of primaquine was limited because of safety concerns, but lower doses had never been tested formally. These findings, that efficacy is retained at a lower dose, imply that primaquine could play an important role in malaria elimination programmes. We now need to evaluate the safety of low-dose primaquine in G6PD-deficient individuals. More questions remain to be answered regarding the best operational strategy for the deployment of primaquine to block malaria transmission."

Co-author Professor Chris Drakeley, Director of the London School of Hygiene & Tropical Medicine's Malaria Centre, said: "This work is a crucial step in the evaluation of primaquine as a malaria transmission blocking intervention. Further work is needed to show reduced infectivity to mosquitoes and to confirm the improved safety of these lower doses."

Professor Moses Kamya of the Infectious Disease Research Collaboration in Kampala, Uganda noted: "This study provides important contemporary information that allows malaria control programmes in endemic countries in Africa to consider the use of primaquine as part of their efforts to deal with this killer disease."

More information: A C Eziefula et al. Single-dose primaquine for

clearance of P. falciparum gametocytes in children with uncomplicated malaria in Uganda: a randomised controlled double-blinded dose-ranging trial. *Lancet Infectious Diseases*. DOI: 10.1016/S1473-3099(13)70268-8