0.40, 0.45, or 0.50 mg/kg dose of primaquine, followed by a 0.50 mg/kg control group of G6PD-replete men. The primary outcome was the within-person percentage change in hemoglobin concentration, assessed using a Hemocue system, from baseline levels between day 0 and day 10. All individuals who received a single-dose of primaquine and completed safety assessments--comprising hemoglobin concentration, urine color, and clinical assessment--daily on days 1-10, and on days 14 and 28 following primaquine administration, were included in the primary sample analysis (n=28). We enrolled 28 participants sequentially, from August 13 to December 19, 2015. Primaquine doses of 0.40, 0.45 and 0.5 mg/kg were all found to be safe and tolerable. A hemolytic dose response was not observed at these doses in any of the participants, no serious adverse events were reported, and adverse events were not associated with the treatment group. SLD-PQ up to 0.50 mg/kg was well tolerated in healthy G6PD-deficient populations in West Africa, and should be rolled out using 0.50 mg/kg as the upper bound for weight-based dosing bands.

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THE ETHICS OF USING A PLACEBO ARM IN RANDOMIZED CONTROLLED TRIALS: A CASE OF IN A PRIMAQUINE ANTIRELAPSE STUDY

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Clinical research involving randomised controlled trials is critical for advancing global health. However global health trials can evoke important ethical issues, particularly the use of placebo or non-intervention control arms. The issue has generated ethical consideration for many years, that hinges on the debate on "double standard of care". We explore this through evaluation of the use of a placebo arm in the specific example of a large multicentred placebo-controlled, double-blinded, randomized trial to determine primaquine antirelapse efficacy in vivax malaria. The trial involves almost 2000 patients enrolled in Indonesia, Vietnam, Ethiopia, Pakistan and Afghanistan. There are three arms - chloroquine or an artemisinin combination therapy treatment plus either: 7 days primaquine , 14 days primaquine or 14 days placebo. The need for the study is justified in view of the poor evidence for the current WHO recommended regimen of 14 days primaquine. The ethical rationale for including a 14-day placebo arm can be made on the grounds that the standard of care in most endemic countries does not include in reality widespread, routine use of primaquine. We argue that since there is equipoise among the study arms, the risk of being in the placebo arm is no greater than the risk of not being in the trial and that there are no double standards. This analysis complements others in literature with regards to the use of placebo or no intervention treatment arms, and highlights that such debate case be justified on its own merits rather than relying on general guidelines.

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INHALED NITRIC OXIDE IMPROVES NEUROCOGNITIVE OUTCOMES IN CHILDREN WITH SEVERE MALARIA AND LACTIC ACIDOSIS

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Severe malaria is a leading cause of neurocognitive impairment in African children. Low levels of bioavailable nitric oxide (NO) are associated with severe malaria. Supplementation with inhaled NO (iNO) has been shown to be neuroprotective in term or near-term infants with persistent pulmonary hypertension but the neuroprotective actions of iNO have not been documented in systemic infections. This randomized, double-blind, placebo-controlled trial compared the effect of inhaled nitric oxide (iNO) at 80ppm versus room air (placebo) on neurocognitive function in children with severe malaria treated with parenteral artesunate. Children aged 1 to 10 years received either iNO or placebo. Six months post-discharge, neurocognitive testing was performed to assess overall cognition, attention, associative memory, executive function, motor skills, language and visual reception. We compared test scores between the treatment arms and the frequency of impairment in all domains between the arms. At six months, 61 children in the iNO arm and 59 children in the placebo arm were evaluated. 35% of children had impairment (defined by a z-score ≤-2SD) in at least one domain. There were no significant differences in z-scores for overall cognition, attention, associative memory and executive function between iNO and the placebo group. Children receiving iNO were less likely to have multiple impaired domains (11.5% vs 25.4%, p=0.048) and to have fine motor impairment, relative to children receiving placebo (8.2% vs 22.0%, p=0.034). Subgroup analysis in children with acidosis at admission showed iNO was associated with improved attention (p=0.001), fine motor functioning (p=0.004), visual reception (p=0.028), receptive language (p=0.015), and overall cognitive function (p=0.009). Inhaled nitric oxide is associated with better cognitive outcomes in children with severe malaria presenting with acidosis.

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A RANDOMIZED TRIAL OF THE SAFETY OF LOW DOSE PRIMAQUINE IN THE TREATMENT OF G6PD NORMAL AND DEFICIENT ADULT PATIENTS WITH *PLASMODIUM FALCIPARUM* MALARIA IN SENEGAL

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WHO recommends the addition of a single dose of primaquine (0.25 mg base/kg) to artemisinin combination treatments (ACTs) as a component of pre-elimination or elimination programs. However, primaquine has been little used in Africa and there are concerns about its safety, as the drug can cause acute haemolytic anaemia in individuals with G6PD deficiency. This open randomised controlled trial was conducted to assess the safety of adding low-dose primaquine to the normal ACT regimen (AL, ASAQ, DHAP) in adult patients in Senegal. Patients with *P. falciparum* malaria (parasitaemia {1,000-100,000} trophozoites/µL) were randomized to receive treatment with ACT or ACT plus low-dose primaquine. Haemoglobin concentration was measured at enrolment, and on days 3, 7, 14, 21 and 28 post-treatment. G6PD status was determined for each patient using a qualitative field test (CareStart™). The primary