

Publication

Effectiveness of rectal artesunate as pre-referral treatment for severe malaria in children under 5 years of age: a multi-country observational study

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BACKGROUND: To prevent child deaths from severe malaria, early parenteral treatment is essential. Yet, in remote rural areas, accessing facilities offering parenteral antimalarials may be difficult. A randomised controlled trial found pre-referral treatment with rectal artesunate (RAS) to reduce deaths and disability in children who arrived at a referral facility with delay. This study examined the effectiveness of pre-referral RAS treatment implemented through routine procedures of established community-based health care systems. **METHODS:** An observational study accompanied the roll-out of RAS in the Democratic Republic of the Congo (DRC), Nigeria and Uganda. Children <5 years of age presenting to a community-based health provider with a positive malaria test and signs of severe malaria were enrolled and followed up during admission and after 28 days to assess their health status and treatment history. The primary outcome was death; covariates of interest included RAS use, referral completion, and post-referral treatment. **RESULTS:** Post-roll-out, RAS was administered to 88% of patients in DRC, 52% in Nigeria, and 70% in Uganda. The overall case fatality rate (CFR) was 6.7% (135/2011) in DRC, 11.7% (69/589) in Nigeria, and 0.5% (19/3686) in Uganda; 13.8% (865/6286) of patients were sick on day 28. The CFR was higher after RAS roll-out in Nigeria (16.1 vs. 4.2%) and stable in DRC (6.7 vs. 6.6%) and Uganda (0.7 vs. 0.3%). In DRC and Nigeria, children receiving RAS were more likely to die than those not receiving RAS (aOR=3.06, 95% CI 1.35-6.92 and aOR=2.16, 95% CI 1.11-4.21, respectively). Only in Uganda, RAS users were less likely to be dead or sick at follow-up (aOR=0.60, 95% CI 0.45-0.79). Post-referral parenteral antimalarials plus oral artemisinin-based combination therapy (ACT), a proxy for appropriate post-referral treatment, was protective. However, in referral health facilities, ACT was not consistently administered after parenteral treatment (DRC 68.4%, Nigeria 0%, Uganda 70.9%). CON-

CLUSIONS: Implemented at scale to the recommended target group, pre-referral RAS had no beneficial effect on child survival in three highly malaria-endemic settings. RAS is unlikely to reduce malaria deaths unless health system issues such as referral and quality of care at all levels are addressed. **TRIAL REGISTRATION:** The study is registered on ClinicalTrials.gov : NCT03568344.

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