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Understanding and improving case management of severe febrile illness in highly malaria-endemic settings: an observational implementation study in the Democratic Republic of the Congo, Nigeria and Uganda

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Introduction

In sub-Saharan Africa, over 400,000 children die annually from malaria and other preventable illnesses. Little is known about where these children die, from which causes, and under which circumstances. A better understanding of these factors is crucial to effectively address the remaining burden of preventable childhood diseases and mortality. Rectal artesunate (RAS) is a potentially life-saving pre-referral treatment for children with severe malaria. However, limited evidence is available regarding the operational feasibility of incorporating RAS into the continuum of care for severe malaria, and the unanticipated consequences, like inappropriate use as artemisinin monotherapy or treatment of uncomplicated malaria, this could have on overall case management.

Methods

The Community Access to Rectal Artesunate for Malaria (CARAMAL) study accompanied the implementation of RAS as a pre-referral treatment in DRC, Nigeria and Uganda. 8,563 children aged <5 years with severe febrile illnesses were detected and enrolled at primary care level, and 6,348 at referral health facilities. The children were followed up during admission and after 28 days to assess healthcare-seeking patterns, RAS use and acceptance, anti-malarial treatment received at the various points of contact with the health system, and health outcomes at day 28.

Ethics

This study was approved by the World Health Organization's Research Ethics Review Committee; the University of Kinshasa School of Public Health Ethics Committee; the Health Research Ethics Committee of the Adamawa State Ministry of Health and the National Health Research Ethics Committee, Nigeria; the Research and Ethics Committee of the Makerere University School of Public Health and the Uganda National Council for Science and Technology; and CHAI's Scientific and Ethical Review Committee.

Results

Post-RAS introduction, RAS was administered to 88% of eligible patients in DRC, 52% in Nigeria, and 70% in Uganda. We followed up 93% of enrolled children (13,870/14,911) 28 days after enrolment at home to determine status and healthcare trajectory. After roll-out, RAS users were less likely to complete referral than RAS non-users in the pre-roll-out phase in DRC (adjusted odds ratio, aOR: 0.48) and Uganda (aOR: 0.72). Post-referral treatment with parenteral artesunate was high (above 80%), but the administration of a full course of artemisinin-based combination therapy to complete treatment as per WHO guidelines was variable (from virtually zero in Nigeria to 65% in DRC). Hence, many children were in fact treated with artemisinin monotherapy. Case fatality rates (CFR) varied largely by country and place of initial presentation (range: 0.3% to 15%). RAS was associated with reduced likelihood of being dead or sick on day 28 only in Uganda (aOR: 0.61, $p<0.05$) where overall CFR was lowest. No protective effect was found in DRC and Nigeria. Most children were considered healthy on day 28, but over 60% had detectable malaria antigenaemia.

Conclusion

For RAS to be an effective pre-referral treatment for children with severe malaria in hard-to-reach locations, underlying health system factors need to be addressed to ensure a functional continuum of care.

Conflicts of interest

None declared.

Aita Signorell is a Scientific Project Leader in the Department of Medicine at the Swiss Tropical & Public Health Institute in Allschwil, Switzerland. Her main research interest lies in the development of medicines for poverty-related diseases and advancing their equitable access through community-centered implementation research and evidence-based decision-making. Dr. Signorell's work has contributed to the development of the first all-oral treatment for both stages of sleeping sickness and approval by the medicines authority of the Democratic Republic of the Congo as well as by the US Food and Drug Administration. Dr. Signorell graduated as a biologist from the University of Basel. She obtained her PhD in biochemistry from the University of Bern, Switzerland, and completed postdoctoral training at the University of Bern and at Weill Cornell Medical College in New York, USA.