Characterisation of febrile non-traumatic coma in sub-Saharan Africa

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Brain infections are important causes of non-traumatic coma, particularly in low-resource areas of Africa and Asia. The WHO Intersectoral Global Action Plan on Epilepsy and Neurological Disorders incorporates neuroinfections (eg, meningitis, encephalitis, HIV, cerebral malaria) in their strategic objectives including "to provide effective, timely and responsive diagnosis, treatment and care".[1] These aspirations are advocated upon well by the two Articles by Stephen Ray and colleagues,[2,3] published in *The Lancet Global Health*, which are timely and of public health importance.

The Articles are complementary. The systematic review[3] synthesises evidence on the morbidity and mortality associated with non-traumatic coma and illustrates the need to invest in advanced tools for diagnosis to optimise treatment and improve outcomes. These gaps in diagnosis and characterisation of features and outcomes of non-traumatic coma are addressed in a real-world scenario in the prospective cohort study[2] conducted in Queen Elizabeth Central Hospital in Blantyre, Malawi.

The systematic review[3] reports that cerebral malaria was the most common cause of non-traumatic coma, most likely due to the recent improvements in the detection and identification of falciparum malaria. Many children survive cerebral malaria, but often with neurological sequelae.[3] Unfortunately, assessment of neurobehavioural outcomes was rarely done in the included studies. These assessments (eg, the Ages and Stages Questionnaire) were often overlooked for non-malarial comas, which are associated with twice the mortality rates of cerebral malaria. The case-fatality rate associated with non-malarial comas remained higher than that for malarial coma after discharge, suggesting the need to invest in post-discharge care for patients with non-malarial coma. Improvements in the assessment and management of neurobehavioral sequelae, including epilepsy, can improve outcomes for all non-traumatic coma. Reduction in reported all-malaria mortality did not occur in cerebral malaria, for which better adjunctive therapies and treatments are urgently required. This finding suggests that mortalities decreased more for other malaria syndromes (eg, malaria with anaemia or with respiratory distress) compared to cerebral malaria.

Improving uptake of viral and bacterial vaccines was acknowledged by Ray and colleagues as one way of addressing the burden of infectious causes of non-malarial coma, but antimicrobial stewardship to prevent treatment resistance needs to be highlighted.[3,4] The reported declining trend for non-traumatic coma of unknown causes—due to increasing use of molecular multiplex diagnostics—is likely to continue, following the increased diagnostic capacity and access to neuroimaging facilities since COVID-19.[3]

Knowledge sharing and exchange programmes can expand research on non-traumatic coma from eastern Africa to other African settings, where comparatively less research is published. Use of standardised definitions and reporting of pathogens and pathophysiological process for non-traumatic coma and validated diagnostic procedures should be encouraged. Strengthening of the health systems in molecular and neuroimaging capacity should also be prioritised.

The prospective study[2] combined novel laboratory, molecular, neuroimaging, and neurobehavioural approaches, to identify and characterise features and outcomes of children with non-traumatic coma. Cerebral malaria was the leading cause of non-traumatic coma, with a prevalence (231 [66%] of 352 children) higher than that estimated by the systematic review (58%);[3] this disparity can be explained by temporal differences and differences in clinical practice between this prospective study and those included in the review. Further, availability of rapid diagnostic tests to complement microscopic parasitaemia in the study (that might have been less accessible in the systematic review studies) will have improved detection of cerebral malaria. Changes in acquisition of immunity following decreases in malaria incidence may have increased the age of children presenting with cerebral malaria. Advances in PCR in this prospective study increased detection of bacterial pathogens compared with use of standard cultures, which was seen most distinctly in patients with acute bacterial meningitis (seven [15%] of 48 *vs* 30 [63%] of 48). These findings established

acute bacterial meningitis as an important cause of non-traumatic coma, and a key driver of poor outcomes in patients with comas of other causes, eg, in malarial comas with bacterial co-infection. Detection of further causes of non-traumatic coma could be increased by widening the panel of organisms detected by PCR. Retinopathy did not distinguish between cerebral malaria with and without other co-infections, perhaps because retinopathy features that are less specific to malaria were included, or because retinopathy resolved before assessment;[5] presumptive cotreatment with antimicrobials should be encouraged in those with malarial coma regardless of retinopathy status.

The high yield of brain parenchyma abnormalities in non-traumatic coma (165 [92%] of 178), with all children with non-malarial coma showing these abnormalities, established the value of MRI in characterisation of neuropathological correlates of non-traumatic coma. Isolation of MRI features specific to distinct comas can create a reference standard for validating new diagnostic biomarkers. The non-specific white lesions observed in those with identified malarial coma are similar to those seen in an epilepsy study,[6] and might have been (in part) due to ongoing seizure activity, which was not examined in the present study. The investigators used a low-field MRI (0.35 Tesla), but stronger magnets could improve the yield.[7]

Neurological sequelae occurred in 50% of children with non-traumatic coma, even though these outcomes are overlooked by many studies.[3] Compared with cerebral malaria, poor outcomes in non-malarial coma could be related to deeper levels of coma, malnutrition, and HIV, as identified in the multivariable models.[2] Chronic illnesses such as HIV and chronic malnutrition, which are associated with neurobehavioural sequelae but not with mortality, are perhaps proxies of consistent health-seeking behaviour in settings with supportive care for these conditions, resulting in increased survival. Prognostic models for mortality can be built from identified physiological factors, such as hyperlactataemia and levels of coma, which were distinct from those of neurological sequelae. Limited investigations in participants might have affected the statistical power or prevented identification of syndromic comorbidities and associated factors.

Findings from this study are a step change in improving the diagnosis, characterisation, and management of non-traumatic coma. The study adds to ongoing efforts to refine diagnosis of non-traumatic coma[8] and screening of neurobehavioural outcomes including epilepsy. It also sets the basis for modelling the effect that policy uptake and implementation of malarial and non-malarial vaccines[9] could have on mortality and morbidity associated with non-traumatic coma. The findings can also support the generation of robust evidence for developing algorithmic criteria for carrying out the investigated diagnostic tests. These efforts will be beneficial in prioritising the distribution of limited resources (eg MRI and PCR) in health facilities and identifying patients who can benefit from prompt referrals based on MRI findings and Integrated Management of Childhood Illness guidelines.[10]

We declare no competing interests.

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1 WHO. Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031. https://www.who.int/publications/i/item/9789240076624 (accessed Feb 16, 2025).
2 Ray STJ, Fuller CE, Ahmadu A, et al. Aetiologies, neuroradiological features, and risk factors for mortality and long-term neurosequelae of febrile coma in Malawian children: a prospective cohort study. *Lancet Glob Health* 2025; published online April 22. https://doi.org/10.1016/S2214-109X(25)00054-3.
3 Ray STJ, Fuller CE, Boubour A, et al. The aetiologies, mortality, and disability of non-traumatic coma in African children: a systematic review and meta-analysis. *Lancet Glob Health* 2025; published online April 22. https://doi.org/10.1016/S2214-109X(25)00055-5.
4 Rice LB. Antimicrobial stewardship and antimicrobial resistance. *Med Clin North Am* 2018; **102:** 805–18.
5 Kariuki SM, Gitau E, Gwer S, et al. Value of *Plasmodium falciparum* histidine-rich protein 2 level and malaria retinopathy in distinguishing cerebral malaria from other acute encephalopathies in Kenyan children. *J Infect Dis* 2014; **209:** 600–09.
6 Kariuki SM, Wagner RG, Gunny R, et al. Magnetic resonance imaging findings in Kenyans and South Africans with active convulsive epilepsy: an observational study. *Epilepsia* 2024; **65:** 165–76.
7 Arnold TC, Freeman CW, Litt B, Stein JM. Low-field MRI: clinical promise and challenges. *J Magn Reson Imaging* 2023; **57:** 25–44.
8 Watson JA, Uyoga S, Wanjiku P, et al. Improving the diagnosis of severe malaria in African children using platelet counts and plasma *Pf*HRP2 concentrations. *Sci Transl Med* 2022; **14:** eabn5040.
9 Osoro CB, Ochodo E, Kwambai TK, et al. Policy uptake and implementation of the RTS,S/AS01 malaria vaccine in sub-Saharan African countries: status 2 years following the WHO recommendation. *BMJ Glob Health* 2024; **9:** e014719.
10 WHO, UNICEF. Handbook IMCI: integrated management of childhood illness. Dec 6, 2005. https://iris.who.int/bitstream/handle/10665/42939/9241546441.pdf (accessed March 29, 2025).