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Simple blood tests may help improve pediatric malaria diagnosis in clinical studies

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Using simple blood tests could help researchers identify children who have been misidentified as having severe malaria, according to a study published today in *eLife*.

Researchers are working to develop better ways to treat severe malaria, which kills about 400,000 children in Africa each year. The discovery could help expedite such research by helping them more accurately identify children with severe malaria. It also reinforces the importance of the World Health Organization's recommendation that all children being treated for severe malaria also receive antibiotics to ensure any misdiagnosed children receive life-saving care.

Diagnosing severe malaria in children in Africa is challenging because the parasites that cause malaria can be found in both healthy and severely ill children. This makes it difficult to tell if the parasites or some other condition is causing illness. In fact, many children diagnosed with severe malaria may have other life-threatening infections. In addition to potentially delaying life-saving antibiotic care, misdiagnosis can skew the results of studies of new treatments for malaria because children misdiagnosed with malaria will not respond, which could make drugs that work look ineffective.

"Inaccuracy in the diagnosis of severe malaria negatively impacts clinical studies, especially those trying to understand which genes may make people more vulnerable to severe disease, or which treatments are most effective," says co-first author James Watson, Senior Scientist at the Mahidol Oxford Tropical Medicine Research Unit (MORU) in Bangkok, Thailand. "We wanted to know whether complete blood count data, notably platelet counts and white blood cell counts, could help make the diagnosis of malaria more accurate."

Watson, along with co-first author Carolyne Ndila, a researcher at The Kenya Medical Research Institute-Wellcome Trust Research Programme (KWTRP), in Kilifi, Kenya, and their colleagues developed a statistical model that could distinguish between severe malaria and other severe illnesses that can be mistaken as severe malaria. To develop the model they included data from over 1,500 children and adults diagnosed with

severe malaria in Thailand and Bangladesh. In these countries, people are rarely misdiagnosed with severe malaria because it is much less common for healthy people to have malaria parasites in their blood.

They applied this model, which relied on platelet and white blood cell counts, to a large cohort of Kenyan children diagnosed with severe malaria. Based on their analysis, they estimate that in approximately one-third of the children, severe malaria was in fact a misdiagnosis.

"Our results support the current guideline that all children with suspected malaria should be given both antimalarials and broad-spectrum antibiotics, as many of the misdiagnosed children will likely have had bacterial sepsis, a severe blood infection," Ndila says.

Using their new model to reanalyse data from clinical studies that looked for potential genetic factors that protect against severe malaria, the team also found that people with glucose-6-phosphate dehydrogenase deficiency probably have some protection from malaria. This benefit was likely obscured in previous studies by the high rate of misdiagnoses.

"We hope our new model can be used by other scientists and clinicians to improve the accuracy of diagnosis in children suspected of having severe malaria," concludes senior author Nicholas White, Professor of Tropical Medicine at Mahidol University. "This will help studies trying to identify better treatments for these patients."

More information: James A Watson et al, Improving statistical power in severe malaria genetic association studies by augmenting phenotypic precision, *eLife* (2021). DOI: 10.7554/eLife.69698

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