

Post-discharge malaria chemoprevention in children with severe anaemia: a robust strategy to save lives



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In low-income countries, and particularly in settings where malaria transmission is high, post-discharge mortality in children remains an underappreciated but significant public health problem, often accounting for a cumulative mortality in the first weeks after discharge similar to that occurring during hospitalisation.^{1,2} Although this phenomenon has been demonstrated to occur in low-income countries irrespective of the reason for admission, certain conditions or comorbidities during admission appear to increase the risk of adverse outcomes post discharge more than others. In this respect, severe anaemia, currently considered the most common cause of malaria-associated mortality globally, is a paradigmatic example of a diagnosis in which susceptibility to adverse outcomes remains high, even after appropriate in-hospital management, including blood transfusions.³ Historically, the scientific community has dealt with such a risk by supplementing anaemic children with iron, hoping that this would contribute to the replenishment of bodily reserves. Albeit with some initial controversial findings, oral iron supplementation is now considered safe and contributes to increasing haemoglobin levels, and is no longer believed to increase the risk of incident malaria or other infections, provided that malaria prevention measures are available in those places where it is routinely provided.⁴ However, and despite its frequent prescription after hospital admissions related to severe anaemia, post-discharge mortality remains unacceptably high.

Little attention has been given to the first weeks post discharge, a period of high vulnerability, and dedicated strategies remain inadequate, resulting in many children at high risk being discharged with no guaranteed follow-up and little or no safety net. In *The Lancet Global Health*, Kamija Phiri and colleagues⁵ report a meta-analysis of three large chemoprevention clinical trials targeting admitted children with severe anaemia in different malaria-endemic countries in sub-Saharan Africa. Their findings indicate that a simple strategy based on repeated monthly pulses of a full antimalarial treatment can very effectively save lives. Indeed, Phiri and colleagues show that post-discharge malaria

chemoprevention is associated with a 77% reduction in mortality (risk ratio 0.23 [95% CI 0.08–0.70], $p=0.0094$, $I^2=0\%$) and a 55% reduction in all-cause readmissions (hazard ratio [HR] 0.45 [95% CI 0.36–0.56], $p<0.0001$). Considering that there was no effect on the prevention of clinic visits for illnesses unrelated to malaria (HR 1.10 [0.98–1.22], $p=0.10$), one could argue that such preventive effects were heavily influenced—albeit not exclusively—by the protective effect provided against newly incident malaria cases.

These notable results were similar, although with differences in the effect size, for different antimalarial drug regimens used for chemoprevention (sulfadoxine–pyrimethamine, artemether–lumefantrine, or dihydroartemisinin–piperaquine) and different durations of treatment, and were limited to the period before protective drug levels had waned. Importantly, the effectiveness of the intervention relied on the combination of drugs used and prevalence of circulating parasites with resistance-conferring mutations, as well as on the duration of post-treatment prophylactic effects attributable to the partner drugs (for example, greater with dihydroartemisinin–piperaquine than with artemether–lumefantrine). The robustness of the study results, already noted for each of the individual clinical trials conducted in the past two decades, has motivated a rather agile positioning by WHO, which now recommends post-discharge malaria chemoprevention for the post-discharge management of children admitted to hospital with severe anaemia living in settings with moderate to high malaria transmission.⁶

Despite these encouraging results, every new successful strategy has to confront its potential flaws. Previous evaluation of the longer-term safety and efficacy of this intervention^{3,7} suggested a potential rebound effect that could be associated with an increase in morbidity and mortality, similar to what has been seen with other chemoprevention strategies. Reassuringly, the meta-analysis by Phiri and colleagues provides stronger evidence in favour of the intervention, given that any prophylactic gains obtained during the weeks in which antimalarials remain effective outweigh the potential detrimental effects once they have waned.

This analysis provides some much-needed insight into post-discharge mortality, a neglected field for the testing of new interventions and for policy recommendations. Still, many questions remain unanswered. What drugs are best suited for it? Should other treatments be given in combination? What should be the exact duration of chemoprevention, and how will this fit into existing strategies, such as seasonal or perennial malaria chemoprevention? Should risk-stratification approaches be put in place to further refine and target those who will most benefit from such an intervention, or should blanket treatment be provided to all patients who are hospitalised with severe anaemia, irrespective of whether malaria was the cause of their anaemia? We hope this excellent work stimulates the curiosity of researchers to continue investigating innovative approaches and opportunities to further reduce child malaria mortality.

We declare no competing interests.

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