despite the low incidence. Donors will eventually have to disburse millions of dollars for each case detected. Finding a way to retain the participation of local populations in screening activities will be crucial when the incidence of HAT becomes very low. The political instability of some endemic countries is worrying.

The animal reservoir is another problem, perhaps the toughest to solve. *T b rhodesiense* is a zoonotic disease and wild animals can serve as vectors for human infections. Unfortunately, *T b gambiense* is found in several domesticated animals (such as dogs, pigs, goats, and sheep).[11,12] The falling number of cases in the past 20 years without any interventions targeting animals shows that this reservoir probably is not important when disease incidence is high, and the actual transmission is then probably higher from humans to animals than the reverse. But at the end of the eradication process when human disease will be rare, the animal reservoir might sustain human infections, which might explain the persistence of low incidence in countries where, assuming a reproduction number lower than 1, the disease should have already disappeared.[6]

Could acoziborole be useful as a veterinary drug, given as mass treatment to all domesticated animals in the residual foci, once a year for 2 or 3 years, with the addition of an attractive scent for each species? The animal feed industry excels at developing foods that could be spiked with acoziborole in the future. Some logistical effort would be required to ensure that each animal ingests a single dose of acoziborole within a given interval, but token compensation for owners who bring animals might be useful (in two regions of the Democratic Republic of the Congo where I lived, a typical village would only hold a few dozen goats and dogs, but usually no pigs or sheep; thus, a day of work would be sufficient to treat all animals). This strategy could be tested in countries in which the number of cases is low but stagnant (5–20 cases per year), such as Guinea, Congo-Brazzaville, Gabon, Chad, and Cameroon,[6] and could be evaluated by monitoring the prevalence of *T b gambiense* among local animals. Gambiense HAT could become the first disease that is eradicated thanks to a drug rather than a vaccine. Let's dream a little!

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Moving towards malaria elimination with safer treatment for children with G6PD deficiency

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"An elephant which kills a rat is not a hero." This African proverb highlights the necessity of moving towards malaria elimination, but not in a way that risks harm to people with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Despite hope following the approval of the first malaria vaccine in 2021, malaria remains the leading cause of death among children in Africa, and is responsible for 10% of the overall disease burden of the continent. Malaria control has stagnated since 2015

and worsened during the COVID-19 pandemic, with a reported 627 000 deaths from malaria in 2020[1] and reports of artemisinin-resistant *Plasmodium falciparum* against a backdrop of widespread insecticide resistance.[2]

The elimination of malaria will undoubtedly require a multifaceted approach. In 2012, noting that all current artemisinin-based combination therapies did not have gametocytocidal activity, WHO recommended that single low-dose primaquine must be given alongside such therapies in low-transmission settings. However, the use of primaquine has been constrained in cases of G6PD deficiency owing to safety concerns. Similar to sickle cell haemoglobin, G6PD deficiency shows strong geographical overlap with malaria, and provides varying levels of protection against malaria infection. At least 230 known G6PD-deficiency variants have been described, affecting over a half a billion people.[3] However, this evolutionary protection is a double-edged sword, as G6PD deficiency predisposes individuals to haemolytic toxicity upon exposure to primaquine and tafenoquine. As such, despite the reported safety of single low-dose primaquine in older children (aged 11–14 years) and adults, and the WHO recommendation that G6PD-deficiency testing is not needed before administration, its uptake has been limited in Africa.[1,4] However, as cases of *Plasmodium vivax* infection have been reported in some areas, the use of single low-dose primaquine could increase, which could hamper malaria-elimination goals—especially in malaria-endemic countries—if the risks of severe haemolysis linked to the use of primaquine prove to be greater than the benefits.

In this issue of *The Lancet Infectious Diseases*, Walter R Taylor and colleagues address a key knowledge gap regarding the safety of single low-dose primaquine: its use in younger children (aged 6 months–11 years) with G6PD deficiency and those with other haemoglobinopathies, including sickle cell disease and thalassemia, which can compound the risks of anaemia.[5] Although children with sickle cell disease are innately protected against classic severe malaria, even submicroscopic or low-parasitaemia malaria infections can lead to severe anaemic crises that are associated with mortality.[6] Taylor and colleagues conducted a trial of single low-dose primaquine dosed on day 0 in combination with a 3-day course of either artemether and lumefantrine or dihydroartemisinin and piperaquine in children with uncomplicated *P falciparum* malaria in two high-transmission sites. The results are encouraging, with 3 (0·3%) of 1121 patients reaching the 5 g/dL haemoglobin concentration threshold, two of whom received primaquine. A decrease in haemoglobin concentration to 5 g/dL certainly warrants clinical concern, and large absolute decreases—even if this concentration is not reached—could also be clinically relevant. The study reached 70% of its target sample size, although the authors are careful to state that despite this shortcoming, the low prevalence of severe anaemia provides further evidence of the safety of single low-dose primaquine in young children, those with sickle cell disease, and those with the *G6PD*-c.202T allele.


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Single low-dose primaquine also led to a significant reduction in gametocytaemia detected by microscopy when used with either artemether and lumefantrine or dihydroartemisinin and piperaquine, despite the novel age-based dosing scheme resulting in doses ranging from 0·07 mg/kg to 0·4 mg/kg, and a median dose lower than the recommended target of 0·25 mg/kg. Whether patients receiving the lower doses of primaquine with dihydroartemisinin and piperaquine can effectively clear gametocytes will be of particular importance, as dose-dependent gametocyte clearance has been observed previously.[7] The feasibility of implementing the age-based single low-dose primaquine regimen alongside artemisinin-based combination therapies, all of which are dosed on the basis of weight, should also be considered. As the use of dihydroartemisinin and piperaquine remains low in Africa, establishing whether single low-dose primaquine remains safe and effective when given with artesunate and amodiaquine, the second most widely used artemisinin-based combination therapy in Africa, will be crucial. Additionally, sulfadoxine and pyrimethamine has been shown to increase gametocyte production and sulfonamides have been associated with a mild haemolytic risk in G6PD deficiency, so assessing the safety of single low-dose primaquine in the context of seasonal malaria chemoprevention with artesunate and amodiaquine and with sulfadoxine and pyrimethamine will be essential. Finally, we note that although the study by Taylor and colleagues was conducted in high-transmission sites to facilitate enrolment, the efficacy and effectiveness of single low-dose primaquine in affecting transmission in such settings is unknown.

Taylor and colleagues should be commended for addressing a knowledge gap regarding an intervention that could reduce malaria transmission in Africa at a time when new tools are desperately needed, and in children who could be at the highest risk of anaemia. In the meantime, we should not lose sight of the need for other novel solutions, including gene therapy, to improve the treatment of patients in Africa with G6PD deficiency and sickle cell disease, which remain neglected tropical diseases despite their tremendous global toll.

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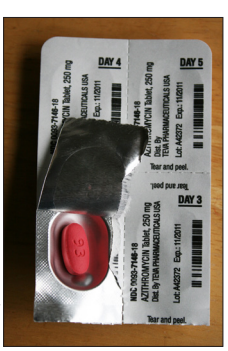
Procalcitonin to reduce antimicrobial overuse in patients with lower respiratory tract infection: time for re-evaluation of our prescription culture?



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WHO has stated that overuse of antimicrobials is the main driver of resistance among microorganisms, leading to fatalities, disabilities, and increased pressure on already challenged health-care systems.[1] For patients admitted to hospital with lower respiratory tract infection, measurement of the biomarker procalcitonin, a 116 amino-acid polypeptide, which can be secreted in most human tissues during bacterial infections,[2,3] has been suggested as a tool to assist clinicians in deciding whether to prescribe antimicrobials.[4] Several randomised controlled trials have aimed to further establish whether such strategies could be effective and safe, however, controversy still exists regarding the efficacy, and adherence to procalcitonin-stopping rules seems crucial to success.[5,6] Trials from several settings have been summarised in meta-analyses, confirming antimicrobial use reduction and safety using procalcitonin algorithms,[7] although safety for critically ill patients has been questioned.[8]

In *The Lancet Infectious Diseases*, Ephraim Tsalik and colleagues[9] report the results of a trial that used a different approach. They randomly assigned patients with lower respiratory tract infection and low procalcitonin concentrations (≤0·25 ng/mL) to receive either oral azithromycin 250 mg or matched placebo for 5 days, to evaluate whether procalcitonin could safely identify patients who would not benefit from antimicrobials. The design is intelligent because it addresses a main limitation in previous trials in the field, adherence to several procalcitonin measurements and reactions on these. The single procalcitonin measurement approach also offers to remove a barrier for implementation, particularly for outpatients, and the point-of-care procalcitonin analysis allows for timely analysis and reduces the need for in-house laboratory infrastructure.

The primary outcome measure was clinical improvement at the day 5 visit, defined as improvement in two or more patient-reported symptoms, absence of deterioration, and absence of a new vital sign abnormality. In the intention-to-treat population, at day 5, 148 (63%, 95% CI 54 to 71) of 238 participants in the placebo group and 155 (69%, 61 to 77) of 227 in the azithromycin group had clinical improvement (between-group difference –6%, 95% CI –15 to 2), and the result