

New antimalarial more effective than current treatment, but no improvement in adverse birth outcomes

March 13 2023



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A large LSTM-led trial confirms new antimalarial, dihydroartemisinin-piperaquine, is more effective at preventing malaria than current WHO

recommended treatment but does not improve adverse birth outcomes.

A large multi-country trial of 4,680 women in sub-Saharan Africa, looking at new antimalarial treatment for [pregnant women](#) in Africa, led by Prof. Feiko ter Kuile, Professor of Tropical Epidemiology, Liverpool School of Tropical Medicine, published the outcomes in *The Lancet* this week.

The trial, known as the IMPROVE trial, confirms the new antimalarial, dihydroartemisinin-piperaquine, is better tolerated, safer, and prevents [malaria](#) more effectively than current WHO recommended treatment but does not improve birth outcomes.

Malaria in pregnancy can have devastating consequences for the mother and developing fetus, resulting in severe anemia in the mother, maternal death, or the mother losing the pregnancy or the baby being born too early or too small. These premature and low birth weight babies have a four times higher risk of dying during their first year.

The WHO currently recommends using a form of malaria prophylaxis called intermittent preventive therapy during pregnancy, or IPTp for short. IPTp is used in 35 countries in sub-Saharan Africa but the [malaria parasite](#) has become increasingly resistant to the only drug currently recommended by the WHO for IPTp: sulfadoxine-pyrimethamine (SP), which threatens its efficacy in east and southern Africa.

In 2003, investigators began a worldwide series of clinical trials to find other antimalarials as suitable alternatives to SP. Out of five candidates evaluated, the antimalarial dihydroartemisinin-piperaquine (DP) was the only candidate tolerated well enough to be considered for further trials. By 2015 it was shown that DP was much more effective than SP in killing malaria parasites or preventing new infections and reducing severe anemia in the mother.

However, these earlier trials were not large enough to determine if this also reduced the risk of babies being born too early or too small. WHO recommended that more research was needed to evaluate the effect of IPTp with dihydroartemisinin-piperaquine on adverse pregnancy outcomes.

In response to this, the LSTM IMPROVE study took place in 12 hospitals in highly malarious areas in western Kenya, northern Tanzania, and southern Malawi, in a multi-country collaboration.

The trial confirmed that the new antimalarial DP was well tolerated, safe, and much more effective than SP. However, the results on birth outcomes were surprising. Despite the apparent superior effect of DP on malaria infections, the risk of adverse pregnancy outcomes was lower, rather than higher, in the SP arm, the arm which has much more malaria during pregnancy.

Successive ultrasound scans revealed that babies showed better fetal growth during pregnancy; the chance of being born with low birthweight was 30% lower in the SP arm. There were no differences in the number of babies born too early, pregnancy loss or early infant deaths. The study also revealed that mothers in the SP arm had better weight gain during pregnancy and better nutritional status at delivery. The results were seen in all three countries, including northern Tanzania, which had the highest rates of SP resistance in sub-Saharan Africa.

A third arm, which included the addition of a single dose of the broad-spectrum antibiotic azithromycin at enrollment to monthly IPTp with DP, did not result in better pregnancy outcomes but increased the incidence of nausea in the mother. Dr. Matthew Chico, Associate Professor at the London School of Hygiene & Tropical Medicine, and co-author, said, "Another surprising finding was that monthly SP was better at reducing the risk of chlamydia, one of the sexually transmitted

diseases we investigated, when compared to azithromycin, which is the standard of care recommended by the WHO."

Dr. Mwayiwawo Madanitsa, senior lecturer and head of department, Clinical Sciences, Academy of Medical Sciences, Malawi University of Science and Technology, and first author, said, "These results suggest that despite the waning antimalarial activity of SP, IPTp-SP continues to provide some benefits, even in areas with very high SP resistance. Our study also shows the importance of well-conducted trials before making policy recommendations."

Feiko ter Kuile, who was the senior author, said, "These results were unexpected as they showed that the new antimalarial was much more effective in treating and preventing malaria infections in pregnancy. However, the babies in the standard of care arm with SP did much better in terms of birthweights, even though the newborns in this arm were born to mothers with double the rate of malaria infections during pregnancy compared to those in the DP arm.

"This is surprising because malaria is one of the most important causes of low birth weight. We now hypothesize that SP has potent non-malarial effects on fetal growth. It does not mean DP had no beneficial effect on birth outcomes, but the non-malarial effects of SP on birthweight may outweigh any improvements in birthweight associated with better prevention from malaria in the DP arm, masking the beneficial effects of DP. We don't yet fully understand how SP promotes maternal gestational weight gain and fetal growth, independent of its antimalarial effects. More research is needed to explore the mechanism."

Whether WHO and countries in East and southern Africa update their recommendation for preventing malaria in pregnancy, in line with the findings, remains to be seen. Feiko ter Kuile continues, "DP is clearly the more effective drug in reducing malaria in [pregnancy](#). So, if the

main goal is to prevent severe malaria and malaria-associated deaths in the mother, DP is the better option. However, another option currently being explored is combining the potent non-malarial effects of SP on fetal growth with the superior antimalarial effects of DP, rather than replacing SP with DP in areas of high SP resistance."

An accompanying commentary in *The Lancet* suggests that studies that combine DP and SP are ongoing in Uganda and Papua New Guinea, and the first results may be available by 2025.

More information: Mwayiwawo Madanitsa et al, Effect of monthly intermittent preventive treatment with dihydroartemisinin–piperaquine with and without azithromycin versus monthly sulfadoxine–pyrimethamine on adverse pregnancy outcomes in Africa: a double-blind randomised, partly placebo-controlled trial, *The Lancet* (2023). DOI: [10.1016/S0140-6736\(22\)02535-1](https://doi.org/10.1016/S0140-6736(22)02535-1)

Abel Kakuru et al, Can we reduce malaria in pregnancy and improve birth outcomes?, *The Lancet* (2023). DOI: [10.1016/S0140-6736\(23\)00101-0](https://doi.org/10.1016/S0140-6736(23)00101-0)

Provided by Liverpool School of Tropical Medicine

Citation: New antimalarial more effective than current treatment, but no improvement in adverse birth outcomes (2023, March 13) retrieved 6 May 2024 from <https://medicalxpress.com/news/2023-03-antimalarial-effective-current-treatment-adverse.html>

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