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The remarkable tenacity of sulfadoxine-pyrimethamine

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Published **Online**
March 25, 2019
http://dx.doi.org/10.1016/S1473-3099(18)30796-5

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Plasmodium falciparum infection during pregnancy causes low birthweight in the newborn, which is a risk factor for infant mortality.[1] Intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine was introduced with the primary aim of ameliorating the effect of malaria on birthweight. At the time of its introduction 15–20 years ago, many countries were still using sulfadoxine-pyrimethamine as the first-line treatment for malaria. Concerns immediately arose about the spread of sulfadoxine-pyrimethamine-resistant malaria and the effect of resistance on the effectiveness of the drug combination for both the treatment and prevention of malaria. Over the past decade, all countries in sub-Saharan Africa have changed their first-line treatment of malaria to an artemisinin-based combination therapy, raising the possibility that sulfadoxine-pyrimethamine resistance might begin to decrease in prevalence. However, in contrast to the re-emergence of chloroquine-susceptible malaria after the removal of drug pressure,[2] sulfadoxine-pyrimethamine resistance seems to be fixed in the parasite population in Africa, despite its withdrawal from use as the first-line treatment for uncomplicated disease.[3] This fixation might be due to the use of sulfadoxine-pyrimethamine for IPTp, or the frequent use of another antifolate drug combination, co-trimoxazole (trimethoprim-sulfamethoxazole), for the treatment of bacterial infection and for prophylaxis among people living with HIV. Regardless of the mechanism of its persistence, sulfadoxine-pyrimethamine resistance seems to be here to stay.

In *The Lancet Infectious Diseases*, Anna Maria van Eijk and colleagues[4] report results of a meta-analysis of aggregated-data from 57 studies (involving 59 457 births) and of individual-patient data from 13 surveys (42 394 births), assessing the effect of sulfadoxine-pyrimethamine resistance on sulfadoxine-pyrimethamine IPTp effectiveness. van Eijk and colleagues collected data on molecular markers of sulfadoxine-pyrimethamine resistance from published reports, individual authors, and population prevalence maps compiled by the Worldwide Antimalarial Resistance Network (WWARN). Data on transmission intensity were collected from the Malaria Atlas Project. The investigators categorised study areas as having low, moderate, or high resistance by exploring various thresholds of prevalence of three mutations in the *P falciparum dhps* gene: Lys540Glu, Ala437Gly, and Ala581Gly. The distribution of sulfadoxine-pyrimethamine-resistant genotypes differed: in east and southern Africa, the high prevalence of *dhps* Lys540Glu defined high-level resistance to sulfadoxine-pyrimethamine, but was rarely identified in central and west Africa, where *dhps* Ala437Gly prevalence distinguished low from moderate levels of resistance. Pooled estimates from the aggregated-data meta-analysis suggested that protection from low birthweight decreases with increasing prevalence of *dhps* Lys540Glu (P_{trend}=0·0060), but is unaffected by the prevalence of *dhps* Ala437Gly mutations (P_{trend}=0·35). The individual-participant analysis of survey data, however, shows the resilience of sulfadoxine-pyrimethamine IPTp, with a protective effect even in areas with a *dhps* Lys540Glu prevalence of more than 90% and Ala581Gly prevalence of less than 10% (relative risk reduction [RRR] 10% [95% CI 7–12%]). This protection waned in areas with both a high prevalence of *dhps* Lys540Glu and a *dhps* Ala581Gly prevalence of 10% or higher (RRR 0·5% [–16 to 14]), but this most extreme resistant genotype was only found in a small number of locations in east Africa.

The need for such a large meta-analysis to link sulfadoxine-pyrimethamine resistance to its protective

efficacy against low birthweight has been clear for many years. Although the failure of sulfadoxine-pyrimethamine to treat and prevent malaria infection during pregnancy has been documented by numerous studies,[5] any effect of the decreased antimalarial efficacy of sulfadoxine-pyrimethamine with respect to birthweight has been difficult to detect. Given the challenges of conducting clinical trials in pregnant women[6] and the variable attributable fraction of malaria to low birthweight,[7] this report shows the catalytic impact that data-sharing platforms, such as those established by WWARN and the Malaria Atlas Project, can have to translate research data into evidence to inform public health.

The results of this study have important implications for the types of data that policy makers require to predict the efficacy of sulfadoxine-pyrimethamine IPTp. In low-resource settings, it might be most beneficial to limit molecular testing to *dhps* Ala581Gly in east and southern Africa and to include *dhps* Ala437Gly in west and central Africa. However, to accurately model the future risk of widespread sulfadoxine-pyrimethamine IPTp failure, we must better understand how resistance emerges and the factors that drive parasite gene flow across geographic regions. Why are quintuple-mutant sulfadoxine-pyrimethamine-resistant parasites so rare in west and central Africa? Why is the highly resistant *dhps* Ala581Gly present in only a few settings and only in the context of the quintuple mutant? What conditions favour or discourage the emergence and spread of sulfadoxine-pyrimethamine-resistant parasites? Previous experience does not provide clear answers to these questions. Although chloroquine-resistant malaria emerged a few times in distinct geographic locations, the genomic analysis of the spread of artemisinin-resistant malaria indicates both independent emergence and also geographic spread.[8] The combination of the types of integrated international database collaborations described by van Eijk and colleagues, along with new methods in genomics and modelling, will allow us to not only track the failure of drugs, but also to be proactive in developing interventions to limit the spread and impact of antimalarial drug resistance.

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We declare no competing interests.

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A new social sciences network for infectious threats

The Ebola epidemic in the Democratic Republic of the Congo (DRC) continues to escalate, new outbreaks of Lassa fever, yellow fever, measles, and other infectious diseases erupt around the world, and antimicrobial resistance intensifies from unmanaged use of these drugs. These infectious threats are intertwined with political and economic instability, changing ecological conditions, livestock management and food production practices, and local communities and their marginalised populations.[1,2] The challenge in addressing these health security threats surpasses conventional response strategies. National governments and international agencies struggle to understand popular reactions to infectious disease emergence and outbreaks and to control deadly diseases.[3]