EDITORIAL

COTRIMOXAZOLE PROPHYLAXIS AND MALARIA IN AFRICA: HAVE THE IMPORTANT QUESTIONS BEEN ANSWERED?

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In 1999, two studies from Abidjan, Côte d’Ivoire showed that daily prophylaxis with cotrimoxazole (trimethoprim-sulfamethoxazole) decreased morbidity in adults with stage 2 or 3 human immunodeficiency virus (HIV) infection and reduced mortality in those co-infected with HIV and tuberculosis, mainly by preventing invasive bacterial infections, chiefly non-typhoid Salmonella and pneumococcus. Malaria infections were also decreased. The opportunistic infections prevented by cotrimoxazole in developed countries, Pneumocystis jiroveci pneumonia and toxoplasmosis, were not prevented in these studies.

Pressure quickly mounted to offer cotrimoxazole prophylaxis to people with HIV throughout Africa. Although some argued that the risks and benefits of cotrimoxazole prophylaxis were likely to be different in settings with different epidemiologic and drug-resistance patterns for opportunistic infections and malaria, others believed that the data from the two Abidjan trials justified stopping ongoing and planned placebo-controlled trials elsewhere in Africa. National policymakers, however, generally believed that they lacked sufficient information for sound policy decisions, and recommendations to offer cotrimoxazole prophylaxis were slow to be adopted and implemented.

Most bacterial infections that were prevented in Abidjan were susceptible to cotrimoxazole. Elsewhere on the continent, most notably in eastern and southern Africa, cotrimoxazole resistance was much more prevalent among bacterial pathogens; in Malawi at that time, 83% of non-typhoid Salmonella and 91% of pneumococcus were resistant. Some policymakers and technical advisors doubted that cotrimoxazole would work as well (or at all) in the face of higher rates of resistance, and worried that widespread cotrimoxazole use would impair the efficacy of sulfadoxine-pyrimethamine (SP), an antifolate antimalarial drug closely related to trimethoprim-sulfamethoxazole, for treating malaria.

Fortunately, some placebo-controlled trials went forward, and the first concern has now been fairly well addressed. Studies in Zambian children and Ugandan adults have demonstrated that the ability of cotrimoxazole to prevent bacterial infection is adequately preserved in the face of high levels of bacterial resistance to preserve morbidity and mortality.

The concerns about cotrimoxazole prophylaxis and malaria treatment and prevention have been harder to address. In vitro studies demonstrated cross-resistance between sulfamethoxazole and sulfadoxine and between trimethoprim and pyrimethamine. The initial fear was that widespread implementation of cotrimoxazole prophylaxis in areas where both HIV and malaria were common would result in selection for antifolate-resistant malaria in the population at large, impairing the efficacy of SP and hastening its demise. Less appreciated but more acutely alarming was the possibility that selection for resistant parasites would occur within malaria-infected individuals taking cotrimoxazole prophylaxis, putting them at increased risk of treatment failure and progression to severe malaria when their malaria was treated with SP.

A clinical trial to directly measure the impact of cotrimoxazole prophylaxis on SP efficacy for the treatment of Plasmodium falciparum malaria was planned in Malawi, but was delayed chiefly out of reluctance to proceed with a placebo-controlled trial in the face of vocal public advocacy in the North for immediate implementation of cotrimoxazole prophylaxis in Africa and recent controversies about the use of placebos in developing countries. This contributed to the impasse between international agencies and advocacy groups calling for implementation “now” and policymakers who wanted setting-specific evidence of benefit.

Thera and others tried to get around this impasse by testing the impact of cotrimoxazole on SP efficacy in healthy children in Mali who had no specific indication for antimicrobial prophylaxis. Cotrimoxazole was a much more highly efficacious antimalarial drug in this setting than expected, with 99% prophylactic efficacy against malaria infection and disease. This was good news, but it meant that there were no cases of malaria in the cotrimoxazole group in which to measure SP efficacy. Molecular markers for antifolate-resistant malaria were measured in the few sub-clinical malaria infections that could be detected in the cotrimoxazole group, and no evidence of selection of antifolate-resistant genotypes by cotrimoxazole prophylaxis was found, but this study was unable to address the efficacy of SP in persons taking cotrimoxazole.

In this issue of the journal, Malamba and others report their attempt to address this question by analyzing malaria parasites from HIV-negative household members of HIV-infected participants in cotrimoxazole prophylaxis trial. Rates of molecular markers for SP-resistant malaria and clinical malaria episodes were compared between household members of an HIV-infected cohort who were receiving daily cotrimoxazole prophylaxis and household members of a second cohort who had not yet been started on cotrimoxazole prophylaxis. Because the cohorts were enrolled in a staggered fashion, the observations of household members of both cohorts were contemporaneous, thus controlling for temporal trends in malaria incidence or SP resistance. The incidence of malaria was significantly lower in the household members of persons receiving cotrimoxazole prophylaxis compared with the control group. The prevalence of infections with molecular markers for SP resistance was similar in both groups.

The creative, impasse-bypassing study design is commendable but leads to some questions. As noted by the investiga-

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tors, if cotrimoxazole prophylaxis in 320 households resulted in a profound and rapid selection for antifolate-resistant malaria, a district-wide increase in SP-resistant genotypes could have already occurred by the time the observations began. Alternatively, a weak selection effect might take longer than a few months to detect. A clean water intervention study was being conducted in the arm receiving cotrimoxazole prophylaxis,12 which could have led to ascertainment bias. Finally, the malaria parasites from HIV-infected index cases were not evaluated, the conclusion that “there is no in vivo selection of cross-resistant parasites by cotrimoxazole” is not directly supported. This conclusion assumes that most malaria transmission takes place between members of the same household. However, the mosquito that bites little sister may be just as likely to be carrying parasites it picked up last week from a neighbor over the hill or across the river as it is to be transmitting parasites from big brother who is HIV-infected and enrolled in a study.

Nevertheless, this study along with the prophylaxis trial in Malian children does offer some reassurance that cotrimoxazole prophylaxis is unlikely to have immediate and catastrophic effects on SP efficacy at the population level. Unfortunately, we still do not know whether SP efficacy for treating or preventing malaria is impaired in the persons who are taking cotrimoxazole prophylaxis. This piece of the puzzle is important to clinicians and policymakers, for two reasons. First, even though most African countries have now changed their malaria treatment policies from SP or chloroquine to artemisinin-based combination therapy (ACT), the substantial lag between policy decisions and successful implementation means that SP is likely to continue to be used for routine treatment of malaria in much of Africa for at least the next few years. Second, intermittent preventive therapy with SP is being used increasingly in pregnant women, infants, and children in the region, and safe, affordable alternatives are lacking. If SP efficacy is impaired among persons receiving cotrimoxazole prophylaxis, a special effort must be made to find alternative antimalarial therapy for them. As ACTs are introduced, those persons receiving daily cotrimoxazole prophylaxis should be targeted for receipt of new drugs where availability of ACTs is limited.

The clinical trials that could have directly and definitively answered the question of the impact of cotrimoxazole prophylaxis on SP resistance and efficacy can no longer be done. More innovative epidemiologic studies like those used by Malamba and others are needed in conjunction with mathematical modeling and molecular evolutionary approaches to understand how drug use affects the rise and dissemination of drug-resistant malaria. In anticipation that cotrimoxazole prophylaxis will guide the next generation of HIV antimicrobial prophylaxis, this conclusion means that SP is likely to continue to be used for routine treatment of malaria in much of Africa for at least the next few years. Second, intermittent preventive therapy with SP is being used increasingly in pregnant women, infants, and children in the region, and safe, affordable alternatives are lacking. If SP efficacy is impaired among persons receiving cotrimoxazole prophylaxis, a special effort must be made to find alternative antimalarial therapy for them. As ACTs are introduced, those persons receiving daily cotrimoxazole prophylaxis should be targeted for receipt of new drugs where availability of ACTs is limited.

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