

CORRESPONDENCE



Effectiveness of Antimalarial Drugs

TO THE EDITOR: In his review article (April 14 issue), Baird¹ states that prescribing “chloroquine . . . in any setting, except one in which its effectiveness has recently been demonstrated, should be considered irresponsible.” As physicians who have worked in rural Zambia, where malaria is endemic, we have witnessed the effect of falciparum malaria on children and are sensitive to Baird’s concerns. However, adults rarely become severely ill. We think that chloroquine remains an inexpensive, rapid-acting drug with few side effects and that it is effective in most patients.

However, recent policy changes removed chloroquine from our formulary on short notice and without an effective and timely alternative. When artemether-based drugs were supplied, the cost, which was 20 to 50 times that of chloroquine, prevented its full implementation or use in patients for whom it was clearly indicated. In addition, the removal of chloroquine made its use in combination with sulfadoxine–pyrimethamine impossible, there-

by eliminating an effective treatment and increasing the chance of the development of resistance to sulfadoxine–pyrimethamine.²

We believe that chloroquine continues to have a useful role in regions where falciparum malaria is endemic and resources are severely limited, even in the face of significant resistance.

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1. Baird JK. Effectiveness of antimalarial drugs. *N Engl J Med* 2005; 352:1565-77.

2. Pitmang SL, Thatcher TD, Madaki JK, Egah DZ, Fischer PR. Comparison of sulfadoxine-pyrimethamine with and without chloroquine for uncomplicated malaria in Nigeria. *Am J Trop Med Hyg* 2005;72:263-6.

TO THE EDITOR: The adapted map in Figure 1 and its legend in Baird’s article are misleading and appear to suggest that the southernmost African countries — South Africa, Swaziland, Lesotho, Botswana, and Namibia — have no malaria. Although these countries have some of the lowest rates of malaria in southern Africa (overall rate, <0.1 person at risk per square kilometer), malaria remains a major cause of disease, death, and poverty there. Despite the presence of malaria-free districts, 10 percent of the people in South Africa and 66 percent of those in Namibia reside in regions with malaria that have stable or unstable (epidemic-prone) transmission of malaria.¹ The resistance of *Plasmodium falciparum* (the main plasmodium parasite) to chloroquine is widespread, resistance to sulfadoxine–pyrimethamine is becoming increasingly common, and multidrug resistance has been reported.²⁻⁴ In these countries with unstable malaria transmission, all age groups are at risk for

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malaria, whereas in the southern African countries with stable malaria transmission (Angola, Comoros, Madagascar, Malawi, Mozambique, Tanzania, and Zambia), children younger than five years of age and pregnant women are at the greatest risk for malaria.

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2. Williams CH, Fredlund VG. Resistant malaria in KwaZulu-Natal. *S Afr Med J* 2002;92:480-1.
3. Roper C, Pearce R, Bredenkamp B, et al. Antifolate antimalarial resistance in southeast Africa: a population-based analysis. *Lancet* 2003;361:1174-81.
4. Schwab U, Allouche A, Doherty JF. Multidrug-resistant malaria from South Africa. *Clin Infect Dis* 2005;40:493.

TO THE EDITOR: Baird states that “mefloquine given as prophylaxis is as well tolerated as other anti-malarial drugs.” Recent trials do not support this view, however. Three randomized, controlled trials of mefloquine prophylaxis in nonmilitary travelers reported an excess of adverse neuropsychiatric effects in the mefloquine groups.¹⁻³ Schlagenhauf and colleagues noted that mefloquine and chloroquine–chloroguanide were associated with similar rates of adverse events and that both regimens showed a trend toward a greater frequency of severe adverse events than did regimens of doxycycline or atovaquone–chloroguanide (12 percent had adverse events with chloroquine–chloroguanide and 11 percent with mefloquine, vs. 7 percent with atovaquone–chloroguanide and 6 percent with doxycycline; $P=0.14$); the frequency of mild-to-moderate adverse effects showed a similar pattern ($P=0.05$, for the comparison of all four treatments).³

Early trials of mefloquine in prisoners and soldiers suggested good tolerability, but the results cannot be generalized to civilian travelers who have very different lifestyles and higher rates of concurrent medication use and coexisting illnesses.⁴ With safer drugs now available, we believe mefloquine should no longer be used as first-line prophylaxis against malaria.

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2. Potasman I, Juven Y, Weller B, Schwartz E. Does mefloquine prophylaxis affect electroencephalographic patterns? *Am J Med* 2002; 112:147-9.
3. Schlagenhauf P, Tschopp A, Johnson R, et al. Tolerability of malaria chemoprophylaxis in non-immune travellers to sub-Saharan Africa: multicentre, randomised, double blind, four arm study. *BMJ* 2003;327:1078.
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DR. BAIRD REPLIES: Gerrish and De Koning express their views about the withdrawal of chloroquine before alternatives become available. The advocated abandonment of chloroquine speaks to the difference between “most” patients with a satisfactory therapeutic response and “all” such patients. Needless suffering occurs in that range of difference between them, be it narrow or wide. The authorities responsible for the decision either to continue or to withdraw chloroquine bear the responsibility for either of those actions, as well as for the provision of alternative therapies.

Smego points to the low risk of malaria across the southern frontier of regions where malaria is endemic on the African continent. The map was based on similar maps published by the World Health Organization (WHO), as noted in the legend; these maps illustrate the locations of appreciable risk. The WHO officers who constructed the original maps undoubtedly applied a threshold of the risk of infection, but one I do not know. The risk of malaria occurs almost anywhere between the polar circles (as outbreaks near North American cities demonstrate). If the risk mentioned by Smego crosses the threshold for the mapping of substantial risk, I hope his letter and this reply will contribute to the improved accuracy of maps in the future.

The recent studies cited by Croft et al. were discussed in my review. We have differences of interpretation. Croft et al. express the view that mefloquine should no longer be used as first-line prophylaxis on the basis of what I consider statistically insignificant ($P=0.14$) differences in the risk of severe adverse events between this and other antimalarial drugs. On the less important issue of mild-to-moderate adverse events, mefloquine and

chloroquine–chloroguanide (a drug combination used successfully by travelers for several decades but now abandoned because of poor protective efficacy) are similar. On the basis of adverse-event profiles, mefloquine clearly is associated with a statistically significant higher risk of neuropsychiatric symptoms than other antimalarial drugs, as I explained in my review. For most travelers who are considered good candidates for mefloquine prophylaxis, including pregnant women and young children, the regimen carries distinct advantages in terms of cost, convenience, proven efficacy, and demonstrated safety. The suggestion that the safety and adverse-event profiles of mefloquine hinge on

very early and limited clinical trials in special populations may mislead readers; mefloquine has been widely used by the traveling public for more than a decade. The responsibility for the decision to recommend mefloquine as first-line or as alternative prophylaxis rests with the national authorities weighing factors of safety, efficacy, cost, and other determinants of effectiveness in the context of the populations they serve.

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Respiratory Syncytial Virus Infection in Elderly Adults

TO THE EDITOR: Falsey et al. (April 28 issue), in their report on respiratory syncytial virus (RSV) infection in elderly and high-risk adults,¹ claim that “the symptoms and signs of RSV infection and those of influenza were not substantially different” and also that the demographic and clinical characteristics of the patients with influenza and of those with RSV infection were similar. If the clinical manifestations of the two diseases were the same, and if the populations that were affected could not be distinguished, how do the authors explain the striking differences between the patients with influenza and those with RSV infection in the rate of office visits (42 percent vs. 17 percent, respectively) and use of antibiotics (33 percent vs. 9 percent)?

Most clinicians make treatment decisions on the basis of a combination of science, experience, and intuition. I suspect that there was some difference that was either not captured or not quantified that influenced both patients’ decisions to see a physician and physicians’ decisions to prescribe an antibiotic.

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1. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infections in elderly and high-risk adults. *N Engl J Med* 2005;352:1749-59.

TO THE EDITOR: Falsey and colleagues probably underestimate the burden of influenza-related mortality among elderly patients. Influenza-related hospitalization often results from secondary bacterial infection that occurs after the virus is cleared, hampering confirmation of the presence of the virus by viral isolation, polymerase-chain-reaction analysis, or serologic studies on admission. Studies of excess mortality,^{1,2} which sidestep the difficulties of case ascertainment, set the current mortality burden associated with influenza in the elderly at three times that of RSV infection.

This point pales, however, beside the fascinating data presented by Falsey et al. on the benefits of influenza vaccine. Vaccine coverage among elderly hospitalized patients with confirmed influenza was 68 percent, as compared with 75 percent among those with RSV infection, indicating that the efficacy of vaccination in preventing influenza-related hospitalizations was only 29 percent (95 percent confidence interval, 2 to 48 percent). A single clinical trial of influenza vaccination in the elderly showed that the efficacy of the vaccine against mild influenza was 57 percent.³ Cohort studies without laboratory confirmation show an astonishing benefit in terms of mortality from all causes in the elderly, but such studies are prone to self-selection bias and overestimation.^{2,4} We think the study by Falsey et al. may come closest to the truth for severe