

for RTS,S are significantly more consistent and encouraging than the data available for SPf66 at any stage of its development. The comparison may not be informative. Nevertheless, we agree with Gosling and Chandramohan that point estimates of vaccine efficacy from phase 2b studies, such as the results we report, are surrounded by uncertainty. RTS,S/AS01E will be evaluated in a wide range of transmission sites and over longer periods of follow-up in a planned phase 3 multicenter efficacy trial.

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## Antimalarial Therapies in Children from Papua New Guinea

**TO THE EDITOR:** In their article on antimalarial combination therapies, Karunajeewa et al. (Dec. 11 issue)<sup>1</sup> conclude that artemether–lumefantrine has more favorable efficacy than dihydroartemisinin–piperazine, even though fat was given with the treatment only in the artemether–lumefantrine group and there was no significant difference in the primary end point. Their per-protocol analysis with a high dropout rate from a small sample results in overestimation of the risk of treatment failure and wide 95% confidence intervals (6.4% to 20.0%). We reanalyzed data from 981 children younger than 5 years of age who were treated with dihydroartemisinin–piperazine in seven clinical trials in Indonesia, Thailand, Uganda, and Burkina Faso. Dihydroartemisinin–piperazine was administered with milk or a biscuit. Overall, the recrudescence rate at day 42 was 3.1% (95% confidence interval, 1.9 to 4.3), ranging from 0 to 7.1%. The risk of recurrent malaria was significantly reduced after treatment with dihydroartemisinin–piperazine as compared with artemether–lumefantrine (odds ratio, 0.51;  $P < 0.001$ ).

Dihydroartemisinin–piperazine is a highly effective treatment for multidrug-resistant falciparum malaria in young children and provides clinically significant post-treatment prophylaxis.<sup>2-4</sup> We recommend that both dihydroartemisinin–piperazine and artemether–lumefantrine be given

with fat (milk, biscuit, or other food) to increase bioavailability.<sup>5</sup>

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Drs. Price and Nosten report serving as consultants to Medicine for Malaria Venture (MMV). No other potential conflict of interest relevant to this letter was reported.

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**THE AUTHORS REPLY:** Enhanced piperazine bioavailability with fat coadministration<sup>1</sup> was reported after our trial had started. There were no food-specific dosing recommendations for dihydroartemisinin–piperazine then or subsequently.<sup>2</sup> Other studies have shown excellent efficacy when fat coadministration was not required, and no pharmacokinetic factors, including baseline parasitemia, were independent determinants of the efficacy of dihydroartemisinin–piperazine in our trial. Nevertheless, because low plasma piperazine concentrations at day 7 predict recrudescence<sup>3</sup> and relevant bioavailability data are from healthy adults,<sup>1</sup> pharmacokinetic studies (including tolerability and safety) determining optimal fat intake in children with falciparum malaria would be valuable. We provided the justification for our sample size, analyzed and interpreted efficacy using current World Health Organization (WHO) guidelines,<sup>4</sup> and presented best-case and worst-case scenarios for the effect of attrition on treatment outcome (see the Supplementary Appendix, available with the full text of the article at NEJM.org). The lower 95% confidence limit for treatment failure with dihydroartemisinin–piperazine at day 42 in per-protocol analyses (6.4%) was above the limit (<5%) recommended by the

WHO for adoption of new therapy.<sup>4</sup> The discordance between this finding and low failure rates in other countries is likely to reflect the epidemiologic complexity of malaria and underscores the need for valid local efficacy trials before new treatments are deployed.

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## Smoking Exposure, 17q21 Variants, and Early-Onset Asthma

**TO THE EDITOR:** Bouzigon et al. (Nov. 6 issue)<sup>1</sup> report that single-nucleotide polymorphisms (SNPs) in the 17q21 region are associated with early-onset asthma in subjects exposed to environmental tobacco smoke. One would predict that environmental factors would have a greater effect in late-onset disease than in early-onset disease. We wonder whether the authors can provide data on SNPs that regulate susceptibility to late-onset asthma when there is passive exposure to tobacco smoke or when the subject is a smoker.

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1. Bouzigon E, Corda E, Aschard H, et al. Effect of 17q21 variants and smoking exposure in early-onset asthma. *N Engl J Med* 2008;359:1985-94.

**THE AUTHORS REPLY:** We have shown that the risk of asthma conferred by genetic variants in chromosome 17q21 is restricted to early-onset asthma and is increased when there is exposure to environmental tobacco smoke in early life. Although we found no association between 17q21 variants and late-onset asthma, we further examined whether the relationship between 17q21 variants and late-onset asthma could be influenced by exposure to environmental tobacco smoke. There were 186 families in which all offspring (with or without late-onset asthma) had exposure to tobacco smoke in early life and 127 families in which all offspring did not have such exposure. We found no association between any of the variants previously investigated and late-onset asthma in exposed or unexposed sibships (Table 1).<sup>1</sup> We conclude that the interaction between the 17q21 locus