To the Editor: The results of the trial reported by Bejon et al. (Dec. 11 issue), in which the malaria vaccine RTS,S/AS01E was administered to children in Kilifi, Kenya, and Korogwe, Tanzania, are impressive. However, there are methodologic issues in the measurement of protective efficacy in sites where the transmission of malaria is falling. In such areas, transmission becomes overdispersed, and measuring protective efficacy against malaria over short periods may be inappropriate. For example, the high protective efficacy of intermittent preventive treatment for malaria in infants that was observed in the first clinical trial in Tanzania was probably exaggerated by a fall in transmission during the trial. Administration of the RTS,S vaccine in adults was shown to give short-lived protection, and in the study by Bejon et al., the incidence of malaria was highest in the placebo group between 3 and 5 months after vaccination. This combination of decreasing transmission and protection over time could lead to an overestimate of efficacy.

Reassuringly, the high protective efficacy was seen in both sites; however, the study was small, the risk of malaria was highly variable, and transmission was falling. Similarly, the SPf66 vaccine showed high protective efficacy in low-transmission but not high-transmission settings. Testing RTS,S in high-transmission sites is a priority in order to refine estimates of SPf66.

Roly D. Gosling, M.D.
Daniel Chandramohan, M.D., Ph.D.
London School of Hygiene and Tropical Medicine
London WC1E 7HT, United Kingdom
roly.gosling@lshtm.ac.uk


The Authors Reply: In response to the comments by Gosling and Chandramohan: overdispersion in malaria is not necessarily limited to areas of falling transmission, and it also occurs in infectious diseases other than malaria. Our reading of the survival plots is of sustained transmission throughout the period of monitoring, although transmission has indeed been falling in the study areas. We certainly agree that estimates of efficacy during long-term follow-up are essential, and such estimates have been made for RTS,S/AS02A, with encouraging results. The data on vaccine efficacy...
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.

Philip Bejon, Ph.D.
Kenya Medical Research Institute
Kilifi, Kenya
pbejon@kilifi.kemri-wellcome.org

Amanda Leach, M.R.C.P.C.H.
GlaxoSmithKline Biologicals
1330 Rixensart, Belgium

International Vaccine Institute
Seoul 151-500, Korea


TO THE EDITOR: In their article on antimalarial combination therapies, Karunajeewa et al. (Dec. 11 issue)1 conclude that artemether–lumefantrine has more favorable efficacy than dihydroartemisinin–piperaquine, 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–piperaquine in seven clinical trials in Indonesia, Thailand, Uganda, and Burkina Faso. Dihydroartemisinin–piperaquine 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–piperaquine as compared with artemether–lumefantrine (odds ratio, 0.51; P<0.001).

Dihydroartemisinin–piperaquine is a highly effective treatment for multidrug-resistant falciparum malaria in young children and provides clinically significant post-treatment prophylaxis.2,4 We recommend that both dihydroartemisinin–piperaquine and artemether–lumefantrine be given with fat (milk, biscuit, or other food) to increase bioavailability.5

Ric N. Price, M.D.
Menzies School of Health Research
Darwin, NT 0811, Australia
rnp@menzies.edu.au

Grant Dorsey, M.D., Ph.D.
University of California
San Francisco, CA 94110

Francois Nosten, M.D., Ph.D.
Shoklo Malaria Research Unit
Mae Sai 63110, Thailand

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.