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CORRESPONDENCE



RTS,S/AS01E Vaccine against Malaria

TO THE EDITOR: The results of the trial reported by Bejon et al. (Dec. 11 issue),¹ 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.² 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.³ Administration of the RTS,S vaccine in adults was shown to give short-lived protection,⁴ and in the study by Bejon et al.,¹ 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-transmission⁵ but not high-transmission settings. Testing RTS,S in high-transmission sites is a priority in order to refine estimates of SPf66.

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THE AUTHORS REPLY: In response to the comments by Gosling and Chandramohan: overdispersion in malaria is not necessarily limited to areas of falling transmission,¹ and it also occurs in infectious diseases other than malaria.² 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.^{3,4} 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.⁵ The data on vaccine efficacy

THIS WEEK'S LETTERS

- 1253 RTS,S/AS01E Vaccine against Malaria
- 1254 Antimalarial Therapies in Children from Papua New Guinea
- 1255 Smoking Exposure, 17q21 Variants, and Early-Onset Asthma
- 1256 Irbesartan for Heart Failure with Preserved Ejection Fraction
- 1259 Medical Mystery: Constipation — The Answer
- 1260 Cytokine Induction after Laboratory-Acquired West Nile Virus Infection

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)¹ 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.²⁻⁴ We recommend that both dihydroartemisinin–piperazine and artemether–lumefantrine be given

with fat (milk, biscuit, or other food) to increase bioavailability.⁵

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