CORRESPONDENCE

RTS,S/AS01 Malaria Vaccine in African Children

TO THE EDITOR: In the article by the RTS,S Clinical Trials Partnership (Nov. 17 issue)[1] on the phase 3 trial of RTS,S (ClinicalTrials.gov number, NCT00866619), an analysis of the efficacy of RTS,S/AS01 against severe malaria was not reported for the vaccine's target age group of infants who were 6 to 12 weeks of age and who received RTS,S with routine childhood vaccines. However, this efficacy can be calculated as 17% (P=0.23) (see Table 1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Therefore, in the age group for whom RTS,S is intended, the efficacy against severe malaria was minimal. This finding was unexpected,[2] and the goal of 50% efficacy against severe malaria of the Malaria Vaccine Technology Roadmap (www.malariavaccine.org/files/Malaria_Vaccine_TRM_Final.pdf) was not met.

Moreover, in the reported 12-month data, there was already significant waning of vaccine efficacy against clinical malaria, and the 17% efficacy against severe malaria in young infants was measured over an average of 7 months. Thus, over longer periods, there will probably be less efficacy. Lower vaccine immunogenicity[3,4] and the rapid waning of induced antibodies and vaccine efficacy[5] shown in phase 2a and field trials[1,4,5] probably contribute to the lower efficacy of RTS,S in young infants. By the time severe malaria develops in infants vaccinated at 2 to 4 months of age (for instance, 7 months after vaccination), vaccine efficacy may be minimal.

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Dr. Hill reports collaborating with GlaxoSmithKline Biologicals and the Program for Appropriate Technology in Health Malaria Initiative to assess RTS,S/AS02 and being a coinventor and codeveloper of other malaria vaccine candidates. No other potential conflict of interest relevant to this letter was reported.

1. RTS,S Clinical Trials Partnership. First results of phase 3 trial of RTS,S/AS01 malaria vaccine in African children. N Engl J Med 2011;365:1863-75.
2. Asante KP, Abdulla S, Agnandji S, et al. Safety and efficacy of the RTS,S/AS01E candidate malaria vaccine given with expanded-programme-on-immunisation vaccines: 19 month follow-up of a randomised, open-label, phase 2 trial. Lancet Infect Dis 2011;11:741-9.
3. Abdulla S, Oberholzer R, Juma O, et al. Safety and immunogenicity of RTS,S/AS02D malaria vaccine in infants. N Engl J Med 2008;359:2533-44.
4. Aide P, Aponte JJ, Renom M, et al. Safety, immunogenicity and duration of protection of the RTS,S/AS02(D) malaria vaccine: one year follow-up of a randomized controlled phase I/IIb trial. PLoS One 2010;5(11):e13838.
5. Guinovart C, Aponte JJ, Sacarlal J, et al. Insights into long-lasting protection induced by RTS,S/AS02A malaria vaccine: further results from a phase IIb trial in Mozambican children. PLoS One 2009;4(4):e5165.

TO THE EDITOR: In the fight against malaria, people must be careful not to overestimate the impact of any single new intervention. I have concerns that the vaccine's researchers "did not observe a reduction in the rate of death from malaria or from any cause" in the vaccine group. I also am concerned that the article may be misleading when the authors state that the "vaccine reduced malaria by half." As a Peace Corps volunteer in Senegal, I saw how news could be misinterpreted in rural villages. In my current pro-

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grams for malaria prevention, I have also seen the positive impact of our work. The hope surrounding this vaccine may tempt populations in malaria-endemic countries to abandon proven methods such as insecticide-treated bed nets. This would be a tragedy, because such public health interventions are working and have been associated with a 20% decrease in deaths from malaria over the past 10 years and with complete eradication of the disease in several countries.[1]

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No potential conflict of interest relevant to this letter was reported.

1. World malaria report 2010. Geneva: World Health Organization, 2010.

TO THE EDITOR: The RTS,S Clinical Trials Partnership describes the favorable interim results of the first large-scale vaccine field trial ever conducted for a human parasitic disease, in this case *Plasmodium falciparum* malaria, which is responsible for most of approximately 655,000 yearly deaths from malaria.[1] We believe that the release of these initial 14-month data showing an approximate 56% reduction in the incidence of first clinical malaria episodes in the older cohort of children (5 to 17 months of age) will enable early consideration of the potential impact of the vaccine in sub-Saharan Africa by public health planners. This consideration will facilitate efficient review by the European Medicines Agency once the trial is complete, accelerating licensure. Should the final results of the study, expected in late 2014,[2] confirm the net benefits seen in this interim analysis, every day saved on the pathway to implementing the RTS,S immunization program will reduce suffering and potentially save lives.

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1. World Malaria Report 2011. Geneva: World Health Organization, 2011:72-4.
2. World Health Organization. Malaria: initiatives for vaccine research (IVR) (http://www.who.int/vaccine_research/diseases/malaria/vaccine_candidate_policy/en/).

THE AUTHORS REPLY: Hill's reanalysis of our data is flawed, and the calculated estimate of vaccine efficacy in the younger age category is incorrect. Hill erroneously assumed that all cases of severe malaria that did not occur during the 12-month postvaccination period in the first 6000 children enrolled in the older age category occurred in the younger age category. He overlooked the fact that an additional 2923 children were enrolled in the older age category and that follow-up extended up to 22 months after vaccination, providing more participants and a longer follow-up period during which cases of severe malaria in these older children contributed to the pooled analysis (see Table 7 in the Supplementary Appendix of our article, available at NEJM.org). Hill incorrectly assigned 187 cases of severe malaria to the younger age category, whereas there were only 66 cases (Table 10a in the Supplementary Appendix).

The lower estimate of vaccine efficacy against severe malaria in the pooled age categories as compared with the first 6000 children in the older age category who were followed for 12 months might be explained by lower vaccine efficacy against severe malaria in the younger age category. A second explanation could be waning protection. Vaccine efficacy in the younger age category will be analyzed later this year, after participants in the younger age category have completed 12 months of follow-up in accordance with our predefined analysis plan. Data on the duration of protection will be available in 2014. The analysis plan was designed to allow dissemination of key findings as soon as they become available, even though this results in our sharing data without being able to fully explain all findings. We think that this approach is worthwhile, since the information we have shared has been useful in stimulating debate in the scientific community and among health authorities on the potential role of this vaccine and in refining forecasts to ensure manufacturing capacity for timely availability of vaccine.

Sherman recognizes the need for continued support for proven methods for malaria prevention, including insecticide-treated bed nets. As emphasized in our article, the RTS,S/AS01 malaria vaccine is not intended as an alternative to established malaria-control measures but rather as an additional tool for integrated control. During the phase 3 RTS,S/AS01 trial, every effort has been made to ensure that all enrolled children sleep under an insecticide-treated bed net. Our

findings thus far show that in a population in which approximately 75% of the children were using insecticide-treated bed nets, cases of clinical malaria were reduced by 55% in the children who received the RTS,S/AS01 vaccine, indicating that the RTS,S/AS01 malaria vaccine could be an important addition to established malaria-control tools.

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The findings and conclusions in this letter have not been formally disseminated by the Centers for Disease Control and Prevention and should not be construed to represent any agency determination or policy.

Since publication of their article, the authors report no further potential conflict of interest.

Escherichia coli O104:H4 Outbreak in Germany

TO THE EDITOR: In their article on last year's outbreak of *Escherichia coli* O104:H4 in Germany, Frank et al. (Nov. 10 issue)[1] report some striking features. Nearly 90% of patients were adults (median age, 42 years), with an overrepresentation of women (68%). In pediatric series, girls also predominate over boys but not to such a marked degree.[2] Moreover, the attack rate of the hemolytic–uremic syndrome associated with diarrhea (845 of 3816 cases, or 22%) in Germany exceeded the rate of 5 to 15% in most previous reports of outbreaks. In children, the administration of antibiotics to empirically treat the prodromal enteritis has been associated with a significantly increased risk of progression to the hemolytic–uremic syndrome.[3,4] This finding is supported by preclinical data in the infection model in the gnotobiotic piglet.[5] The pattern of antibiotic use to treat bloody diarrhea may differ between children and adults. This may explain the high proportion of patients with the hemolytic–uremic syndrome in the German outbreak, independent of the pathogenicity of the unusual bacterial strain. Clarification of antibiotic use to treat the antecedent enteritis may shed light on this particular outbreak and help guide the prescription of antibiotics in patients with gastroenteritis and bloody diarrhea.

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No potential conflict of interest relevant to this letter was reported.

1. Frank C, Werber D, Cramer JP, et al. Epidemic profile of Shiga-toxin–producing *Escherichia coli* O104:H4 outbreak in Germany. N Engl J Med 2011;365:1771-80.
2. Trachtman H, Cnaan A, Christen E, et al. Effect of an oral Shiga toxin-binding agent on diarrhea-associated hemolytic uremic syndrome in children: a randomized controlled trial. JAMA 2003;290:1337-44.
3. Wong CS, Jelacic S, Habeeb RL, Watkins SL, Tarr PI. The risk of hemolytic–uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 infections. N Engl J Med 2000;342:1930-6.
4. Pavia AT, Nichols CR, Green DP, et al. Hemolytic-uremic syndrome during an outbreak of Escherichia coli O157:H7 infections in institutions for mentally retarded persons: clinical and epidemiological observations. J Pediatr 1990;116:544-51.
5. Zhang Q, Donohue-Rolfe A, Krautz-Peterson G, et al. Gnotobiotic piglet infection model for evaluating the safe use of antibiotics against Escherichia coli O157:H7 infection. J Infect Dis 2009;199:486-93.

THE AUTHORS AND A COLLEAGUE REPLY: Trachtman hypothesizes that the frequent use of antimicrobial drugs in adults may explain the unusually high proportion of patients with the hemolytic–uremic syndrome in the German outbreak of Shiga-toxin–producing *E. coli* O104:H4 infection. The outpatient use of antimicrobial drugs in Germany is low as compared with international standards,[1] and the administration of such drugs is generally not recommended for the empirical treatment of acute (bloody) diarrhea. In the case of Shiga-toxin–producing *E. coli* infection, it is recommended that practitioners refrain from administering antimicrobials.[2,3] In hypothesis-generating interviews that we conducted early in the outbreak investigation, only 6 of 36 adult patients with the hemolytic–uremic syndrome (17%) for whom data were available reported having taken antimicrobials in the course of their illness or having received a corresponding prescription. This finding is consistent with treatment regimens reported to us by many hospitals and specific recommendations issued dur-