Antimalarial Therapies in Children from Papua New Guinea

N Engl J Med 2009; 360:1254-1255 March 19, 2009 DOI: 10.1056/NEJMc090023

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

Lorenz von Seidlein, Ph.D.
International Vaccine Institute
Seoul 1S1-500, Korea

1. Smith DL, Dushoff J, Snow RW, Hay SI. The entomological inoculation rate and Plasmodium falciparum infection in African children. Nature 2005;438:492-5.
2. Woolhouse ME, Dye C, Etard JF, et al. Heterogeneities in the transmission of infectious agents: implications for the design of control programs. Proc Natl Acad Sci U S A 1997;94:338-42.
3. Okiro EA, Hay SI, Gikandi PW, et al. The decline in paediatric malaria admissions on the coast of Kenya. Malar J 2007;6:151.
4. O'Meara WP, Bejon P, Mwangi TW, et al. Effect of a fall in malaria transmission on morbidity and mortality in Kilifi, Kenya. Lancet 2008;372:1555-62.
5. Alonso PL, Sacarlal J, Aponte JJ, et al. Duration of protection with RTS,S/AS02A malaria vaccine in prevention of Plasmodium falciparum disease in Mozambican children: single-blind extended follow-up of a randomised controlled trial. Lancet 2005; 366:2012-8.

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–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 Sod 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.

1. Karunajeewa HA, Mueller I, Senn M, et al. A trial of combination antimalarial therapies in children from Papua New Guinea. N Engl J Med 2008;359:2545-57.
2. Ratcliff A, Siswantoro H, Kenangalem E, et al. Two fixed-dose artemisinin combinations for drug-resistant falciparum and vivax malaria in Papua, Indonesia: an open-label randomised comparison. Lancet 2007;369:757-65.
3. Yeka A, Dorsey G, Kamya MR, et al. Artemether-lumefantrine versus dihydroartemisinin-piperaquine for treating uncomplicated malaria: a randomized trial to guide policy in Uganda. PLoS ONE 2008;3(6):e2390.
4. Ashley EA, McGready R, Hutagalung R, et al. A randomized, controlled study of a simple, once-daily regimen of dihydroartemisinin-piperaquine for the treatment of uncomplicated, multidrug-resistant falciparum malaria. Clin Infect Dis 2005;41: 425-32.
5. Sim IK, Davis TM, Ilett KF. Effects of a high-fat meal on the relative oral bioavailability of piperaquine. Antimicrob Agents Chemother 2005;49:2407-11.

THE AUTHORS REPLY: Enhanced piperaquine bioavailability with fat coadministration[1] was reported after our trial had started. There were no food-specific dosing recommendations for dihydroartemisinin–piperaquine then or subsequently.[2] 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–piperaquine in our trial. Nevertheless, because low plasma piperaquine concentrations at day 7 predict recrudescence[3] and relevant bioavailability data are from healthy adults,[1] 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,[4] 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–piperaquine at day 42 in per-protocol analyses (6.4%) was above the limit (<5%) recommended by the WHO for adoption of new therapy.[4] 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.

Timothy M.E. Davis, D.Phil., M.B., B.S.
University of Western Australia
Crawley, WA 6009, Australia
tdavis@cyllene.uwa.edu.au

Harin A. Karunajeewa, M.B., B.S.
Western Hospital
Footscray, VIC 3011, Australia

Ivo Mueller, Ph.D.
Papua New Guinea Institute of Medical Research
Madang 511, Papua New Guinea

1. Sim IK, Davis TM, Ilett KF. Effects of a high-fat meal on the relative oral bioavailability of piperaquine. Antimicrob Agents Chemother 2005;49:2407-11.
2. Duo-Cotecxin antimalarial. Beijing: Beijing Holley-Cotec Pharmaceuticals Co. Ltd. (Accessed February 18, 2009, at http://www.cotecxin.com/en/products/antimalarial/Combination/2008-09-24/Combination35i74i271.html.)
3. Price RN, Hasugian AR, Ratcliff A, et al. Clinical and pharmacological determinants of the therapeutic response to dihydroartemisinin-piperaquine for drug-resistant malaria. Antimicrob Agents Chemother 2007;51:4090-7.
4. Assessment and monitoring of antimalarial drug efficacy for the treatment of uncomplicated falciparum malaria. Geneva: World Health Organization, 2003. (WHO/HTM/RBM/2003.50.)

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

TO THE EDITOR: Bouzigon et al. (Nov. 6 issue)[1] 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.

Hiroyuki Morita, M.D., Ph.D.
Ryozo Nagai, M.D., Ph.D.
University of Tokyo
Tokyo 113-8655, Japan
hmrt-tky@umin.net

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).[1] We conclude that the interaction between the 17q21 locus