Heat-Stable Oral Rotavirus Vaccine

TO THE EDITOR: Isanaka and colleagues (March 23 issue)[1] tested a heat-stable rotavirus vaccine in Niger and report an efficacy of 66.7% against severe rotavirus gastroenteritis in the per-protocol population. The purpose of rotavirus vaccination is ultimately to reduce the incidence of diarrhea and diarrhea-related death. However, the rate of severe gastroenteritis due to any cause was not significantly lower among the vaccinated infants than among those who received placebo (difference in rate, 1.97 cases per 100 person-years; 95% confidence interval [CI], −1.28 to 5.22). The lack of efficacy against severe gastroenteritis has not been highlighted in the discussion although this information is crucial for decision makers. The intention-to-treat analysis more closely reflects efficacy in real-world conditions. Everyone who received the first dose of vaccine was included in the intention-to-treat analysis; 86% of them went on to receive all three doses per the protocol and were included in the per-protocol analysis. In the intention-to-treat analysis, there was a significantly higher rate of gastroenteritis due to any cause in the vaccine group than in the placebo group (difference in rate, −6.59 cases per 100 person-years; 95% CI, −11.89 to −1.29 [negative difference values favor the placebo group]). Again, there was no benefit of the vaccine against severe gastroenteritis. This vaccine could aggravate the problem it is meant to solve in resource-poor countries.

Jaspreet Kaur, M.B., B.S.
Jacob Puliyel, M.D.

St. Stephen's Hospital
Delhi, India
puliyel@gmail.com

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THE AUTHORS REPLY: Kaur and Puliyel highlight the importance of rotavirus vaccination, but we disagree that the purpose of rotavirus vaccination is to reduce the incidence of all-cause diarrhea and diarrhea-related death. Rotavirus vaccination is intended to reduce the incidence of diarrhea and diarrhea-related death caused by rotavirus. However, because rotavirus is known to be the single largest contributor to diarrhea morbidity in some geographic settings,[1] it is not surprising that large-scale vaccination can have an important effect on the overall burden of diarrhea. Experience from contexts in which rotavirus vaccination has been provided at large scale suggests a positive effect on the incidence of hospitalization, clinic visits, and diarrhea-related death.[2]

Sheila Isanaka, Sc.D.
Harvard T.H. Chan School of Public Health
Boston, MA

Ali Djibo, M.D.
University of Niamey
Niamey, Niger

Rebecca F. Grais, Ph.D.
Epicentre
Paris, France
rebecca.grais@epicentre.msf.org

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

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Sickle Cell Disease

TO THE EDITOR: The review of sickle cell disease by Piel et al. (April 20 issue)[1] is timely and highlights the need to address the lack of research about this disease in sub-Saharan Africa. The authors rightly state that in the past two decades, childhood mortality has been reduced in sub-

Saharan Africa, but the survival data cited by Piel et al. were derived from a single-site study performed almost four decades ago.[2]

Two-year follow-up data from a pilot cohort study in Nigeria (Table 1) show that survival among children with sickle cell disease remains poor in sub-Saharan Africa.[3] There are no conclusive data to support the use of chemoprevention in addition to insecticide-treated bed nets for prophylaxis against malaria in patients with sickle cell disease.[4]

With regard to Figure 3 in the review by Piel et al., multiple data suggest that the Cameroon haplotype of the β-globin gene (*HBB*) is associated with a more severe phenotype than the Benin haplotype; thus, in the figure, the Cameroon haplotype should have been to the right of the Benin haplotype. In addition to fetal hemoglobin (HbF)-promoting loci and the coinheritance of α-thalassemia that are established genetic modifiers of sickle cell disease, data also provide support for genetic risk markers of renal dysfunction in *APOL1* and *HMOX1*[5] and of cholestasis in *UGT1A1*.

Baba Inusa, F.R.C.P.C.H., D.C.P. (Hematology)

Guy's and St. Thomas' NHS Foundation Trust
London, United Kingdom
baba.inusa@gstt.nhs.uk

Joyce Popoola, F.R.C.P., Ph.D.

St. George's University Hospitals NHS Foundation Trust
London, United Kingdom

Ambroise Wonkam, Ph.D., D.Med.

University of Cape Town
Cape Town, South Africa

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Table 1. Two-Year Follow-up of Infants Who Received a Diagnosis of Sickle Cell Disease at 0 to 6 Months of Age.*

Finding	Infants with Sickle Cell Disease (N=48)	Controls (N=96)	Total (N=144)
	number (percent)		
Alive	26 (54)	72 (75)	98 (68)
Died	1 (2)	1 (1)	2 (1)
Family relocated	12 (25)†	7 (7)	19 (13)
No telephone in home	6 (12)	13 (14)	9 (13)
Family's telephone switched off	3 (6)	3 (3)	6 (4)

* Data are from the Sickle Cell Cohort Study: A Sustainable Pilot Scheme (http://www.migration4development.org/en/projects/sickle-cell-cohort-study-sustainable-pilot-scheme) conducted in Abuja, Nigeria.
† P=0.003 for the comparison with controls.

TO THE EDITOR: In their review article, Piel et al. omit the role of the human immunodeficiency virus (HIV) in sickle cell disease and the interaction between it and HIV infection. Because the HIV epidemic has spread to every country where sickle cell disease is prevalent, this interaction has become a crucial topic.[1]

Several studies suggest that sickle cell disease may slow the progression of HIV infection, and recently the hemolytic conditions of sickle cell disease were shown to up-regulate hypoxiic response and iron regulatory pathways leading to the inhibition of HIV type 1 replication.[1,2] However, concomitant HIV infection may increase the frequency and the severity of conditions that are naturally associated with sickle cell disease. For instance, stroke, pulmonary arterial hypertension, and avascular necrosis are observed to be worse and more frequent in patients with sickle cell disease who are receiving antiretroviral therapy for HIV infection than in those who do not have these conditions.[3] Immunosuppression from HIV infection may further affect the natural history of infections in sickle cell disease, modifying the disease presentation and the incidence of those infections. All these interactions may affect patients with both HIV infection and sickle cell disease.

Michele Bibas, M.D.

Lazzaro Spallanzani National Institute for Infectious Diseases
Rome, Italy
michele.bibas@inmi.it

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

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TO THE EDITOR: In their review article on sickle cell disease, Piel et al. do not clearly indicate that sickle cell anemia and hemoglobin SC (HbSC) disease are two different variants, with different pathophysiologic features, clinical presentations, treatments, and life expectancies.[1] Of note, in HbSC disease, the hemolysis rate is low and the occurrence of vasculopathy-associated strokes, pulmonary hypertension, leg ulcers, and nephropathy is rare. Indeed, the hemoglobin level exceeds 10 g per deciliter in 90% of patients, and hyperviscosity is the predominant mechanism underlying complications. Sex is the main genetic determinant of disease severity, since women are protected by menstrual iron depletion.[1]

Phlebotomy is safe and effective in preventing life-threatening thrombosis events, whereas its effect on sensorineuronal complications remains unknown. The most appropriate care for millions of patients with HbSC worldwide is an important issue.

François Lionnet, M.D.
Jean-Philippe Haymann, Ph.D., M.D.
Claude Bachmeyer, M.D.

Hôpital Tenon
Paris, France
francois.lionnet@aphp.fr

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

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TO THE EDITOR: Piel et al. summarize the factors contributing to improved clinical outcomes in patients with sickle cell disease. An important omission from this otherwise excellent review is the association of cranial moyamoya arteriopathy with sickle cell disease.[1] As many as 43% of patients with sickle cell disease and strokes may have intracranial stenoses and collateral vessels that indicate the moyamoya syndrome, and among such patients the risk of stroke is up to five times as high as the risk among patients without these changes.[2] Patients in this subgroup may continue to have strokes despite the most appropriate long-term transfusion regimen, and in these patients, surgical revascularization of the brain can provide a clinically significant and durable reduction in the risk of stroke.[3] The role of cranial revascularization is supported by the most recent guidelines of the American Heart Association Stroke Council, and high-volume centers have had the best outcomes.[4,5]

Awareness of the possibility of the moyamoya syndrome in the population with sickle cell disease should facilitate timely referral for surgical evaluation and treatment. We think this awareness will further improve the outcomes of patients living with this condition.

Edward R. Smith, M.D.
Matthew Heeney, M.D.
R. Michael Scott, M.D.

Boston Children's Hospital
Boston, MA
edward.smith@childrens.harvard.edu

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

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TO THE EDITOR: The review article on sickle cell disease by Piel et al. served as a reminder of the staggering worldwide burden of this disorder and of the hemoglobinopathies in general. Lessons from the remarkable success reported[1,2] in the avoidance and prevention of β-thalassemia in Sardinia underscore the importance of preconception

genetic counseling, carrier detection, and prenatal and preimplantation genetic diagnosis. There is an equivalent need for this approach to sickle cell disease. Clinicians are required as part of the expected standard of care to offer carrier testing specifically to black Americans, among whom the risk of being a carrier of the sickle cell mutation is approximately 1 in 10. Couples who are identified as being carriers of this mutation must also be offered prenatal genetic testing in established pregnancies and preimplantation genetic testing in planned pregnancies.[3]

Aubrey Milunsky, M.D., D.Sc.
Center for Human Genetics
Cambridge, MA
amilunsky@chginc.org

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

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THE AUTHORS REPLY: We are delighted to see that our review article on sickle cell disease has prompted positive comments about the timeliness of the article and the neglect of the important worldwide burden of this disease. We fully agree with Inusa and collaborators that survival among children with sickle cell disease in sub-Saharan Africa remains poor. Up-to-date data from large-scale studies on this neglected issue are lacking. With regard to the severity of the Cameroon and Benin haplotypes, although some studies have shown that levels of hemoglobin F might be marginally lower in the Cameroon haplotype than in the Benin haplotype, clinical data on phenotypic differences remain limited. It is therefore possible that the order of these two haplotypes might be reversed for certain clinical complications. The ability of haplotypes to predict clinical severity is limited and appears to be entirely mediated through effects on hemoglobin F levels.

We welcome the suggestions by Bibas about possible omissions in our article regarding the role of HIV, as well as the suggestions by Lionnet and colleagues regarding differences between subtypes of sickle cell disorders, particularly HbSC. Smith et al. note the association of cranial moyamoya arteriopathy with sickle cell disease, and Milunsky describes the importance of preconception genetic counseling, carrier detection, and prenatal and preimplantation genetic diagnosis. These suggestions all highlight the complexity of sickle cell disease and of its prevention and management. Most of the specific points made in these letters would have required at least some contextual information to guide the readers, which was not possible owing to space constraints. We had to make rigorous choices about the content of this review, and we attempted to keep a global focus throughout.

Frédéric B. Piel, Ph.D.
Imperial College London
London, United Kingdom
f.piel@imperial.ac.uk

Martin H. Steinberg, M.D.
Boston University School of Medicine
Boston, MA

David C. Rees, F.R.C.P.C.H.
King's College London
London, United Kingdom

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Artemisinin-Resistant *Plasmodium falciparum* in Africa

TO THE EDITOR: Lu et al. (March 9 issue)[1] report on an artemisinin-resistant *Plasmodium falciparum* strain in Africa. We advise caution.

Blood levels of dihydroartemisinin were not reported. Parasitemia on day 3 was low (1 parasite per 200 white cells) and could have been caused by pyknotic parasites. The authors do not indicate the variations among the ring-stage survival assays used with a culture-adapted CWX isolate. Culture-adapted parasites can differ from source populations.[2]

The period of 8 weeks between the patient's return from Africa and the diagnosis of falciparum malaria was unusually long. A single