Severe Malaria in African Children — The Need for Continuing Investment

Kathryn Maitland, M.B., B.S., Ph.D.

In large parts of sub-Saharan Africa, the start of the seasonal rains means that within weeks, hospitals will witness a sharp upsurge in admissions to their pediatric wards. Many children who are admitted will be suffering from life-threatening complications of *Plasmodium falciparum* malaria, such as coma and convulsions (cerebral malaria), severe anemia (requiring urgent lifesaving transfusion), and rapid breathing (due to severe metabolic acidosis). Approximately 90% of the world's falciparum infections and deaths occur in sub-Saharan Africa, the latter almost entirely in children younger than 5 years of age.

Few of these children will ever be cared for in intensive care or high-dependency units, so most will rely instead on simple supportive treatments and parenteral antimalarial agents to avert death. Even with the rapid administration of the best available antimalarial drugs, at least 1 in 10 children admitted to hospitals in sub-Saharan Africa with severe and complicated malaria dies. About 1200 children die from malaria in this region every day,[1] accounting for the vast majority of the 631,000 deaths annually on the continent (see Gething et al. in this issue of the *Journal*, pages 2435–2445). To put these figures into perspective: in absolute terms, annually a similar number of children in Africa die from malaria as die globally from pneumonia, the leading cause of death in children after the neonatal period.

The news is not all bad. Over the past decade there has been an unprecedented increase in funding for malaria-control activities, including a major scale-up in the distribution of bed nets treated with long-lasting insecticides and the widespread introduction of and improved access to effective artemisinin combination treatments. As a result, the disease has retreated from large parts of the globe. Nevertheless, malaria remains stubbornly unyielding in sub-Saharan Africa and in some parts of Asia. Today, 57% of Africans live in areas that continue to have moderate-to-high rates of malaria transmission, with 10 countries accounting for 87% of people exposed to the highest-intensity malaria transmission in the world.[2] The ongoing transmission reflects inadequate implementation of control and early-treatment measures by the poorest countries with the weakest health system infrastructures in Africa, as indicated by Gething et al.

Moreover, the emergence and spread in many parts of Africa of mosquito resistance to all classes of insecticides threatens the effectiveness of the control measures that are in place. The urgency of the threat of widespread insecticide resistance is underlined in the *Global Plan for Insecticide Resistance Management in Malaria Vectors* published by the World Health Organization and the Roll Back Malaria Partnership in 2012, which also emphasizes the fact that currently there are no readily available alternatives to the pyrethroids available for wide-scale public health application.

Furthermore, there are also no current fallback drugs in the pipeline for malaria treatment should artemisinin-combination treatments start to fail in Africa. The emergence of artemisinin resistance in Southeast Asia, emanating from the border areas between Thailand and Cambodia, is a major global concern. The historical increase in resistance to the previous first-line antimalarial treatments chloroquine and sulfadoxine–pyrimethamine has been chronicled; that resistance also originated in western Cambodia and then spread across Asia into Africa, resulting in the deaths of millions of children.

Finally, a highly effective malaria vaccine remains a long way off. Early optimism that the most promising vaccine candidate developed to date (RTS,S) would reduce the burden of severe and fatal malaria has proved premature, with the most recent report of long-term follow-up data (to 48 months) revealing waning vaccine efficacy and an increased risk of severe malaria beginning 20 months after vaccination.

At a clinical level, infants and young children in malaria-endemic African countries typically have many episodes of uncomplicated malaria before they acquire protective immunity. The majority of these episodes are associated with fever and malaise and resolve with oral artemisinin-combination

treatment, but some cases progress to severe disease. Severe malaria is a complex, multisystem disorder with a clinical presentation that shares many complications with severe sepsis.

Over the past decade, there has been some progress in defining best practices for antimalarial treatment. The Artesunate versus Quinine in Severe Malaria in African Children Trial (AQUAMAT), conducted in 9 African countries and involving 5425 children, showed that artesunate-treated children had a 22.5% (95% confidence interval, 8.1 to 36.9) lower relative risk of death than those receiving the time-honored quinine.[3] Even such fairly modest mortality improvements can result in huge net benefits: if artesunate treatment were widely implemented, the 2.5% absolute survival advantage over quinine could mean averting the deaths of 100,000 African children every year.

I was the lead investigator in the only other large, multicenter trial focused on severe malaria, the Fluid Expansion as Support Therapy (FEAST) trial. In that phase 3, randomized, controlled trial involving 3141 African children, bolus resuscitation with either saline or albumin increased the absolute risk of death by 3 to 4% over that associated with care involving no fluid bolus.[4] What that means on the ground has been captured in a short video, in which a girl is brought to the emergency department of a resource-limited hospital in eastern Uganda with coma, shock, and severe acidosis from severe malaria.[5] As the result of the FEAST trial, she does not receive the fluid bolus that would ordinarily have been given for shock management, and she can be seen toward the end of the film in her village, singing with her friends, a disability-free survivor of severe malaria. Although a difference in outcome of 3 to 4% may sound modest, it could translate into tens of thousands of lives lost owing to a recommendation for fluid-bolus resuscitation.

These studies demonstrate that high-quality trials can be undertaken — and can have a substantial effect on malaria outcomes. Indeed, the slow progress in this field is astonishing, given that malaria has been around for millennia and has been a major force for human evolutionary selection, shaping the genetic profiles of African populations. Contrast this pace of change with our progress in the treatment of HIV, a disease a little more than three decades old: there, sustained investment has led to robust clinical characterization, multiple clinical trials generating new knowledge, and dramatic improvements in outcome throughout Africa and the world. Whereas substantial investments have been made in malaria-prevention strategies and antimalarial treatment, management of the complications of severe malaria has been largely neglected as a strategic priority. A search of the clinical-trial registration sites ClinicalTrials.gov and ISRCTN for planned or ongoing large-scale trials in severe malaria identified only one phase 3 trial, a multicenter trial of blood-transfusion strategies (ISRCTN84086586). There thus seems little prospect of further reducing the substantial mortality burden from severe malaria in the foreseeable future.

To break this impasse, there is an urgent need to catalyze and accelerate the severe-malaria research agenda, including the conduct of trials designed to be more efficient by addressing multiple questions more rapidly, to ultimately improve the outcomes of severe malaria infections among African children.

Disclosure forms provided by the author are available at NEJM.org.

From the Wellcome Centre for Clinical Tropical Medicine, Imperial College, London.

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