recruiting 26,296 children [1, 2]. Mortality risk varied between 1.4% and 9.5%, with the lowest figures for Blantyre and Lambaréné, the sites where the current trial was implemented. Mortality rates associated with severe malaria can vary several fold among sites: in the Artesunate versus Quinine (AQUAMAT) study, 1 site had a mortality risk of 4.3% (18/422 fatal cases; 95% confidence interval [CI], 2.5%–6.7%) [3]; this is comparable to the risks observed in our study (per protocol analysis, 1.2% (2/171 fatal cases; 95% CI, .14%–4.2%).

We were careful not to recommend that artesunate dosing practices be changed on the basis of our results and, instead, suggested that further studies be pursued. These studies are underway in our SMAC network. We will also aim to derive results for the intramuscular route of administration [4], which has been relatively neglected until now.

The original recommendations to change from a conventional quinine treatment regimen to one that uses a loading dose on admission were made almost 3 decades ago on purely pharmacokinetic grounds [5]. The quinine loading dose regimen was included in guidelines without the benefit of a mortality study. Now, for the first time, we are assessing artesunate using similar pharmacokinetic and dynamic approaches.

Parasite clearance times are viewed as “weak and unvalidated surrogate” endpoints in this context, although Dondorp et al have reported elsewhere that prolongation of parasite clearance times is useful when trying to understand artesunate resistance [6]. We suggest that prolonged parasite clearance times can be viewed as representing a relative reduction in artesunate efficacy. Thus, if parasite clearance rates are comparable, then artesunate efficacy is also comparable.

Dondorp et al argue that parasite clearance rate is not a critical parameter of drug efficacy because fatal cases of malaria have parasite clearance rates that are comparable with those of survivors. An alternative interpretation of these (unpublished) findings is that the patients were dying of secondary complications, reflecting processes unlikely to be reversed by antimalarial treatment. It is worth recalling that in uncomplicated malaria, parasite clearance data were the basis for White’s group to suggest that 4 mg/kg of oral artesunate should be given once a day; this observation was made after studying 8 dosing regimens in 47 patients [7].

Theoretical arguments (based on our own studies [8]) suggest that schizonts are relatively less sensitive to artemisinins, but are not entirely “refractory.” We said that “in patients presenting with severe malaria whose parasite burdens would be of variable age distribution and synchronicity, the artemisinin derivatives would have a greater likelihood of inhibiting the current parasite cycle than other drugs either by interrupting the maturation of ring forms into the more pathogenically important trophozoites, or by inhibiting the metabolic processes of mature stages already sequestered and the development of early schizonts into segmenters” [8]. The exposure to dihydroartemisinin in patients with malaria far exceeds the concentrations required to kill parasites in vitro. Consequently, even in cases with parasite stages that are relatively less sensitive, thresholds for killing are easily achieved, particularly with the higher dose we have studied. We have provided the World Wide Antimalarial Resistance Network with the individual patient data from our study so that colleagues may be able to refine their models for parasite clearance kinetics.

Woodrow and Taylor question an element of our experimental design, that is, the selection of a 20% value of delta. The primary endpoint of the proportion of patients achieving >99% parasite reduction in 24 hours is an extremely stringent one, and our calculations assumed that approximately 70% of
children would achieve this rate of clearance (implying that in course 30% would not). Children who may not have achieved this primary endpoint for clearance nevertheless have comparable overall parasite clearance rates between treatment regimens, as confirmed in the secondary parasite clearance estimates we reported. Delta values should allow for the variability associated with a particular endpoint measurement, as well as biologically useful differences. The probability of observing a difference in proportions between the 3- and 5- dose treatments of ~10% units, assuming the null hypothesis is true, is 0.1 for an intention to treat analysis.

The authors voice different opinions regarding the relationship between parasite clearance rates and survival. Dondorp and colleagues suggest that parasite clearance data do not relate to clinical outcomes, whereas Woodrow and Taylor interpret our results to suggest that there is an accompanying likelihood of clinical detriment in the form of increased mortality if there is prolongation in parasite clearance. Resolving these issues may need more work. Meanwhile, we will continue assessing dose and route optimization strategies for parenteral artesunate in severe malaria in appropriately regulated trials.

Note

Disclaimer. The opinions expressed herein are those of the authors and do not necessarily reflect the opinions of their institutions, or official policy or opinions of the US Department of the Army.

Potential conflicts of interest. J. M. and S. D. are employed by the Medicines for Malaria Venture as stated in the affiliations. P. W. and R. S. M. are employed by the US Army, which holds an investigational new drug application (IND) with the US Food and Drug Administration for this product. S. K. has been a consultant to GlaxoSmithKline and Sanofi Aventis. All other authors report no potential conflicts.

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Yamikani Chimalizeni,1 Kondwana Kawaza,7 Marielle K. Bouyou Akoté,5 Mathias Dusch,1,2 Benjamin Mordmüller,1,2 Katrin Kösters,1 Alexander Humberg,1 R. Scott Miller,8 Peter Weina,1 Stephan Duparc,3 Jörg Mührle,9 Jürgen F. J. Kun,3 Tim Planche,2,10 Paktiya Tejasivasadharm,11 Julie Anne Simpson,12 Carsten Köhler,1 and Sanjeev Krishna2,10

1 Institut für Tropenmedizin, Universität Tübingen, Wilhelmstraße 27, Tübingen, Germany; 2 Medical Research Unit, Albert Schweitzer Hospital, Lambardé, Gabon; 3 Blantyre Malaria Project, University of Malawi College of Medicine, Blantyre 3, Malawi; 4 College of Osteopathic Medicine, Michigan State University, East Lansing, Michigan; 5 Département de Parasitologie, Mycologie et Médecine Tropicale, Faculté de Médecine et des Sciences de la Santé, Libreville BP 4009, Gabon; 6 Malawi/Liverpool/Wellcome Trust Clinical Research Programme, University of Malawi College of Medicine, Blantyre, Malawi; 7 Department of Paediatrics, Queen Elizabeth Central Hospital, Blantyre, Malawi; 8 Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Silver Spring, Maryland; 9 Medicines for Malaria Venture, International Centre Centrin, Geneva, Switzerland; 10 Division of Clinical Sciences, Centre for Infection, St. George’s University of London, United Kingdom; 11 Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand; and 12 Centre for MEGA Epidemiology, School of Population Health, University of Melbourne, Melbourne, Australia


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Correspondence: Sanjeev Krishna, Division of Clinical Sciences, Centre for Infection, St. George’s University of London, London SW17 0RE, United Kingdom (s.krishna@bgul.ac.uk).

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Peter Gottfried Kremsner,1,2 Terrie Taylor,3,4 Saadou Issifou,1,2 Maryvonne Kombila,5

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