Transactions of the Royal Society of Tropical Medicine and Hygiene (2006) **100**, 615—622

available at www.sciencedirect.com

SCIENCE DIRECT®

journal homepage: www.elsevierhealth.com/journals/trst

Standardized data collection for multi-center clinical studies of severe malaria in African children: establishing the SMAC network

Terrie Taylor[a,*], Christopher Olola[b], Clarissa Valim[c], Tsiri Agbenyega[d], Peter Kremsner[e,f], Sanjeev Krishna[g], Dominic Kwiatkowski[h], Charles Newton[b,i], Michel Missinou[e], Margaret Pinder[j], David Wypij[c],

on behalf of the SMAC network

[a] *Department of Internal Medicine, College of Osteopathic Medicine, Michigan State University, E. Lansing, MI, USA*
[b] *Centre for Geographic Medicine Research-Coast, Kenya Medical Research Institute, Kilifi, Kenya*
[c] *Children's Hospital, Clinical Research Program, 300 Longwood Avenue, Boston, MA 02115, USA*
[d] *Department of Physiology, School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana*
[e] *Albert Schweitzer Hospital, Lambaréné, Gabon*
[f] *Department of Parasitology, Institute of Tropical Medicine, University of Tübingen, Germany*
[g] *Department of Cellular and Molecular Sciences (Infectious Diseases), St. George's Hospital Medical School, London SW17 0RE, UK*
[h] *Wellcome Center for Human Genetics, Roosevelt Drive, Oxford OX3 7BN, UK*
[i] *Institute of Child Health, London, UK*
[j] *Medical Research Council Laboratories, Malaria Research Programme, P.O. Box 273, The Gambia*

Received 18 May 2005; received in revised form 21 September 2005; accepted 22 September 2005
Available online 23 March 2006

KEYWORDS
Malaria;
Severe malaria;
Plasmodium falciparum;
Children;
Clinical trials;
Africa

Summary The Severe Malaria in African Children (SMAC) network was established to conduct mortality-based trials. Although falciparum malaria kills more than one million children each year, single centers cannot enroll enough patients to detect reductions of 20—30% in mortality rates. Our aim was to quantify and describe severe malaria across a variety of epidemiological settings so that we could design intervention studies with more precise sample size estimates. We used a standardized surveillance mechanism to capture clinical, laboratory and outcome data on all parasitemic children admitted to hospital. Between December 2000 and December 2003, 20 333 patients were enrolled at five sites. The frequency of severe malaria syndromes

* Corresponding author. Present address: Department of Internal Medicine, B309-B W. Fee Hall, E. Lansing, MI 48824, USA. Tel.: +1 517 353 3211; fax: +1 517 432 1062.
E-mail address: taylort@msu.edu (T. Taylor).

doi:10.1016/j.trstmh.2005.09.021

(cerebral malaria, severe malarial anemia and acidosis) differed between sites, as did the syndrome-specific mortality rates. Intervention studies targeted at reducing mortality in one or a combination of severe malaria syndromes would require 3—4 years to complete within the existing network. These data provide more accurate estimates of the disease burden of children hospitalized for malaria in sub-Saharan Africa. Networks are required to recruit enough patients for mortality-based studies and to encompass the epidemiological diversity of malaria in sub-Saharan Africa. SMAC represents the first effort to develop this capacity.

1. Introduction

Malaria kills over a million African children each year, but there are few definitive studies of life-saving interventions. The disease is distributed widely across the continent and a hospital that treats 10 000 children with malarial illness may see only 100—200 fatal cases each year (Greenwood et al., 1991). Individual research centers cannot recruit sufficient numbers of patients for large-scale clinical trials capable of detecting 20—30% reductions in case fatality rate. In addition, few surrogate markers for a fatal outcome have been identified and animal models do not mimic human disease closely enough to reliably evaluate new treatments (Newton et al., 1998). For these reasons, multi-center studies are required to identify interventions that reduce mortality.

The importance of establishing pan-African networks to study various aspects of malaria was recognized at an international, multidisciplinary meeting held in Senegal in 1997 (Bruno et al., 1997). We identified all clinical malaria research groups in Africa that had published intervention studies involving children with severe falciparum malaria in peer-reviewed journals and invited them to join a clinical trials network. Five sites responded, and with support from a US National Institutes of Health-funded planning grant, representatives from each participated in a series of meetings in 1997 and 1998, culminating in a research proposal to the NIH in September 1998. The award to support 'Severe Malaria in African Children (SMAC): A Clinical Network' was made through a cooperative agreement mechanism in September 1999.

The main objective of the network is to reduce the mortality of severe malaria in African children by supporting the conduct of definitive clinical trials across the continent. Published comparative studies indicate that there is considerable variation in the frequencies and mortality rates of different severe malaria syndromes (Snow et al., 1997). Because children with severe malaria require treatment with parenteral drugs, the network population consists of hospitalized children. This is a select, heterogeneous group, but these patients do reflect severe malaria in each setting, they represent the group most likely to participate in future clinical trials and they encompass much of the epidemiological diversity of malaria across the continent (Snow et al., 1994).

In this paper, we describe the mechanisms employed to establish the network and to assess data quality. We also compare the characteristics of the patients and the pattern of severe malaria across study sites.

2. Methods

2.1. Organization

SMAC was funded under a cooperative agreement awarded by the National Institute of Allergy and Infectious Diseases (30 Sept 1999—31 Aug 2004). The primary awardee, Michigan State University, subcontracted to the participating field sites: Banjul (Medical Research Council Laboratories, Malaria Research Programme, Banjul, The Gambia); Blantyre (Blantyre Malaria Project, Queen Elizabeth Central Hospital, Blantyre, Malawi); Kumasi (University of Science and Technology, School of Medical Science, Kumasi, Ghana); Kilifi (Kenya Medical Research Institute for Geographic Medicine Research-Coast (KEMRI/CGMR), Wellcome Trust Research Laboratories, Kilifi, Kenya) and two sites in Gabon, Lambaréné and Libreville, both administered by the Medical Research Unit, Albert Schweitzer Hospital, Lambaréné, Gabon. A subcontract was also awarded to the biostatistical core (Children's Hospital, Clinical Research Program, Boston, Massachusetts, USA).

Michigan State University served as the administrative coordinating center and was responsible for arranging travel, managing the list serve, tracking various versions of protocols, developing case report forms, expediting communication and overseeing finances. Each site was responsible for its data collection and entry; assistance was provided by the Data Coordinator (CO), based at the SMAC site in Kilifi, Kenya.

The first task was to develop a core database in order to identify all parasitemic children admitted to the hospitals at each study site and to document the distribution of the established disease syndromes (cerebral malaria, severe malarial anemia, acidosis) and their outcomes (survived, died or absconded).

Identifying all children admitted with malaria infection (i.e. with *Plasmodium falciparum* parasitemia) requires a constant presence in the admissions area and the ability to stain and interpret blood films around the clock. Additional SMAC staff members were required at some sites to ensure that all parasitemic children admitted to each hospital were identified and, if informed consent was forthcoming, were included in the database.

The patient populations were expected to differ across sites. The Albert Schweitzer Hospital in Lambaréné is a private hospital with 30 beds for children. The hospitals in Banjul, Libreville, Kumasi and Blantyre are all government teaching institutions for local medical schools and have 158, 65, 184 and 200 inpatient pediatric beds respectively. Kilifi