REDEFINING CEREBRAL MALARIA

A multi-centre study of Malarial Retinopathy

Kalifa Bojang
and Terrie Taylor
on behalf of the SMAC network
Severe Malaria in African Children (SMAC) Network Sites

- Banjul, The Gambia
- Kumasi, Ghana
- Kilifi, Kenya
- Lambaréné, Gabon
- Blantyre, Malawi
Why do we need a network?

- Severe malaria is a relatively rare event, so statistical power is gained most efficiently by involving multiple sites.

- Epidemiology of malaria is too diverse to rely on findings from a single site.

- Mortality-based studies of human malaria are required because animal models are inadequate and no clinical surrogate measures have been identified.
### Characteristics of SMAC Sites

<table>
<thead>
<tr>
<th>Study Site</th>
<th>Type of hospital</th>
<th>Peds beds</th>
<th>Peak Transmission Season(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banjul, Gambia</td>
<td>Public, central</td>
<td>158</td>
<td>J F M A M J J A S O N D</td>
</tr>
<tr>
<td>Blantyre, Malawi</td>
<td>Public, central, teaching</td>
<td>200</td>
<td>J F M A M J J A S O N D</td>
</tr>
<tr>
<td>Kilifi, Kenya</td>
<td>Public, central, district</td>
<td>41</td>
<td>J F M A M J J A S O N D</td>
</tr>
<tr>
<td>Kumasi, Ghana</td>
<td>Public, central, teaching</td>
<td>184</td>
<td>J F M A M J J A S O N D</td>
</tr>
<tr>
<td>Lambaréne Gabon</td>
<td>Private</td>
<td>30</td>
<td>J F M A M J J A S O N D</td>
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SMAC goals

• Develop methods for acquiring standardized data in multiple sites

• Improve descriptions of disease syndromes
  - Epidemiology
  - Clinical trials
  - Genetic studies

• Provide estimates of disease burden

• Conduct large, simple mortality-based studies of promising interventions conducted according to GCP and GLP guidelines
Clinical spectrum of *P. falciparum* malaria (infants and young children)

- Sporozoite inoculation
  - Asymptomatic parasitaemia
    - Clinical malaria
      - Severe malaria
        - Death

Factors:
- Immunological
- Environmental
- Genetic
- Antimalarials

Symptoms:
- SMA, respiratory distress
- Prostration, convulsion
- Hypoglycaemia, coma

Counts:
- 400
- 200
- 100
- 2
- 1
Malawi autopsy study

An ongoing autopsy-based study of fatal cerebral malaria in one of the SMAC sites (Blantyre, Malawi) suggests that clinical case definition of CM
- *P. falciparum* parasitemia
- Blantyre Coma Score < 3
- No other obvious cause of coma (i.e., meningitis, hypoglycemia,
- post-ictal state)
is incorrect nearly 25% of the time
Autopsies in 41 children meeting clinical case definition of CM revealed that:

- 32 pts had no identifiable cause of death other than sequestration ("true CM")
- Unsuspected causes of death were found in 9 pts and only one had parasite sequestration ("faux CM")
- Ocular funduscopy was the best clinical indicator of cerebral sequestration
  - 31/32 "true CMs" had + eye findings
  - 1/9 "faux CMs" had + eye findings
Eye findings and their relationship to outcome

- **(a) Retinal whitening**
  - 50% of children with clinically defined CM
  - RR of death: 3 (95% CI 1–8)

- **(b) Hemorrhages**
  - 35-40% of children with clinically defined CM
  - NOT associated with a poor outcome

- **(c) Retinal vessel abnormalities**
  - Seen in 25% of children with clinically defined CM
  - RR of death: 3 (1–10)

- **(d) Papilledema**
  - 8-10% of children with clinically defined CM
  - RR (death): 7 (95% CI 3–17)
Validating this single-site observation

• The only reliable clinical indicator of ‘true’ cerebral malaria in the Malawi autopsy study was the presence of at least one of the four elements of the ‘malarial retinopathy’, visible on either direct or indirect ophthalmoscopy.

• Can this observation be validated elsewhere in Africa?
If so, could the clinical case definition of cerebral malaria be improved by including ocular fundus findings?
Objectives

Primary objective:
• To evaluate the utility of ocular fundus findings, as
determined by a trained non-ophthalmologist clinician, in
identifying which of the patients who satisfy the standard
clinical case definition of cerebral malaria during life
actually have histological evidence of sequestration after
death

Secondary objectives:
• To assess the prognostic value of the ocular fundus findings
in predicting adverse outcomes in patients with clinically
defined cerebral malaria

• To evaluate the accuracy of a simple measure of cerebral
sequestration (brain smear) compared to the ‘gold standard’
(cerebral histology).
Study design

• Prospective observational cohort study at 5 SMAC study sites, in children less than 12 years

• 1,964 children will be enrolled over 48 months

• Routine treatment for cerebral malaria per national treatment guidelines at each site
Inclusion/exclusion criteria

**Inclusion criteria**

1. *P. falciparum* parasitemia (any density)
2. Blantyre Coma Score < 3
3. No other obvious cause of coma (e.g., hypoglycemia, meningitis, post-ictal state).
4. Age ≤ 144 months.
5. Informed consent of parent/guardian.

**Exclusion criterion**

1. Inability to perform the ophthalmological examination within 6 hours of admission.
Investigations

• Fingerpick blood sample to determine parasitaemia, anaemia, lactate and blood glucose concentration

• Direct and indirect opthalmoscopic exam (on fully dilated pupils) within 6 hours of admission:
  - Papilledema
  - Hemorrhages
  - Whitening
  - Vessel changes

• In the event of a death, permission will be sought to collect a sample of frontal lobe by puncturing the supraorbital plate
  - Gold standard ("true" vs "faux") assessment of sequestration
Brain smears

- Traditionally, the sequestration of *P. falciparum*-infected red cells in the micro-circulation of the brain has only been demonstrated histologically, using brain tissue collected at post mortem.

- Full autopsies are not possible at all of the SMAC sites.

- To facilitate the collection of brain tissue to test our hypothesis, supra-orbital sampling will be carried out.
• Brain sample
• Frontal lobe, via supra-orbital plate
• A core of brain tissue is obtained
  • Smears (for immediate staining)
  • Formalin fixation (for histology, later)
• No disfiguring marks on the face
Histology and smears

- Supraorbital tissue will be fixed in formalin, and subjected to the usual histological examination (in Blantyre)
- Smears will be prepared, stained and analyzed on site and in Blantyre
  - Smears and histology will be compared
  - Can sequestration be reliably identified by smears?
- If so, this is a technique applicable in any hospital that can carry out peripheral smears for malaria
The SMAC team

- **Gabon**: Michel Missinou, S. Issifou, Pierre Blaise Matsiegui, Bertrand Lell, Steffen Borrmann, Sanjeev Krishna, Tim Planche, Maryvonne Kombila, Nestor Obiang, Frankie Mbadinga and Arnaud Dzeing, **Peter Kremsner**

- **The Gambia**: I. Abubakar, Emmanuel Onyekwelu, David Ameh, Janet Fullah, Abdou Bah, Pamela Esangbedo, Jally-Mori Njie, Margaret Pinder, **Kalifa Bojang**

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- **Harvard School of Public Health/Children’s Hospital**: Clarissa Valim, David Wipj.

- **Michigan State University**: Rebecca Elsesser, Lori Ashmann, Rebecca Gleason, Paula Holzheuer, Jim Lorenz, Terrie Taylor