Severe malaria: management with few resources

Kath Maitland

Imperial College London
&
KEMRI / Wellcome Trust Programme, Kilifi, Kenya
**Plasmodium falciparum** malaria

In African children <5 years

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Parasite positive</td>
<td>50%</td>
</tr>
<tr>
<td>Mild clinical disease</td>
<td>1-2 episodes / year</td>
</tr>
<tr>
<td>Hospital admission</td>
<td>10% / year</td>
</tr>
<tr>
<td>Severe disease</td>
<td>10%</td>
</tr>
<tr>
<td>Mortality</td>
<td>5-40%</td>
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**Malaria-specific mortality** 1-2%
Elimination

Malaria Elimination 1

Shrinking the malaria map: progress and prospects

Richard G A Feachem, Allison A Phillips, Jimee Hwang, Chris Cotter, Benjamin Wielgosz, Brian M Greenwood, Oliver Sabot, Mario Henry Rodriguez, Rabindra R Abeyasinghe, Tedros Adhanom Ghebreyesus, Robert W Snow

In the past 150 years, roughly half of the countries in the world eliminated malaria. Nowadays, there are 99 endemic countries—67 are controlling malaria and 32 are pursuing an elimination strategy. This four-part Series presents evidence about the technical, operational, and financial dimensions of malaria elimination. The first paper in this Series reviews definitions of elimination and the state that precedes it: controlled low-endemic malaria. Feasibility assessments are described as a crucial step for a country transitioning from controlled low-endemic malaria to elimination. Characteristics of the 32 malaria-eliminating countries are presented, and contrasted with countries that pursued elimination in the past. Challenges and risks of elimination are presented, including *Plasmodium vivax*, resistance in the parasite and mosquito populations, and potential resurgence if investment and vigilance decrease. The benefits of elimination are outlined, specifically elimination as a regional and global public good. Priorities for the next decade are described.

- aggressive control of transmission (ITBN and insecticides)
- new treatments and diagnostics
- investment in vaccine development
Shrinking the map?
2000: 218 million African citizens exposed to very high levels of malaria endemicity

2010: reduced to 183 million

✓ 57% African populations live in countries with moderate or high transmission

✓ 2010: WHO estimated 580,000 deaths severe malaria in African children

✓ ~90% of the world’s severe and fatal malaria affects young children in sSA

Noor et al, 2014 Lancet
Elimination—are we nearly there yet?

• Changing landscape of malaria risk – more complex than predicted by models
• Larges areas reporting no change, increased or resurgence of malaria after sustained control
• Vaccines development............
RTS,S vaccine 40-month efficacy against (mild) clinical malaria:

- Children 5-17mths (36.3%; 32–401), or 28.3% (23.3–32.9) without the booster;
- Children aged 6–12 weeks protection: 26%; 20–32), or 18% 12–24% without the booster.
- No evidence of protection from severe malaria or mortality
- **Evidence of delayed increased risk of severe malaria > 20 months in non-booster strategy**

➢ Role out: extra immunisation visits (vaccine and booster doses)
Defining severe malaria in African children and progress with management
Soroti Hospital, Eastern Uganda
> 8000 admissions per year
What defines paediatric severe malaria?

Severe malaria syndromes

Cerebral Malaria

Severe anaemia
Multi-organ disease?
INDICATORS OF LIFE-THREATENING MALARIA IN AFRICAN CHILDREN

Kevin Marsh, M.B., Ch.B., Dayo Forster, Ph.D., Catherine Waruiru, M.B., Ch.B., Isiah Mwangi, M.B., Ch.B., Maria Winstanley, M.B., Ch.B., Victoria Marsh, M.B., Ch.B., Charles Newton, M.D., Peter Winstanley, M.D., Peter Warn, F.I.M.L.S., Norbert Peshu, M.B., Ch.B., Geoffrey Pasvol, M.D., and Robert Snow, Ph.D.

Abstract  Background. Above one million deaths from malaria are in African children each year. The recognition and management of life-threatening malaria has not been validated in them.

Methods. We conducted a retrospective study of clinic data to identify children admitted to the pediatric ward of a tertiary hospital with a primary diagnosis of malaria, and prospectively monitored the frequency and mortality associated with the World Health Organization (WHO) definition of severe malaria. A logistic-regression analysis identified the greatest prognostic value from four variables: impaired consciousness, severe respiratory distress, severe anemia, and jaundice.

Results. We studied 184 (1 to 120 months) with a primary diagnosis of malaria. Of these, 54 were among those who died. The mortality rate was 29.3% (95% confidence interval, 20.7% to 38.7%). The deaths occurred in children with malaria, the presentation of whom was associated with a higher risk of death. (N Engl J Med 2006;355:1481–90.)
AQUAMAT study sites

• Mozambique: Beira
• Kenya: Kilifi
• The Gambia: Banjul
• Ghana: Kumasi
• Tanzania: Korogwe and Muheza
• Uganda: Mbarare
• Nigeria: Ilorin
• Ruanda: Rwamagana
• DRC: Kinshasa
What defines severe malaria?

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\(^1\) Von Siedle Predicting Outcome CID 2012

* Church Maitland Systematic Review Bacterial Co-infection in malaria BMC Medicine 2014
Predicting the Clinical Outcome of Severe Falciparum Malaria in African Children: Findings From a Large Randomized Trial

Lorenz von Seidlein,1 Rasaq Olaosebikan,2,3 Ilse C. E. Hendriksen,4 Sue J. Lee,4 Olanrewaju Timothy Adedoyin,5 Tsiri Agbenyega,6 Samuel Blay Nguah,6 Kalifa Bojang,2,3 Jacqueline L. Deen,1 Jennifer Evans,6 Caterina I. Fanello,4 Ermelinda Gomes,7 Alínia José Pedro,7 Catherine Kahabuka,8 Corine Karema,9 Esther Kivaya,10 Kathryn Maitland,10 Olugbenga A. Mokuolu,5 George Mtove,11 Juliet Mwanga-Amupaire,13 Behzad Nadjm,12 Margaret Nansumba,13 Wirichada Pan Ngum,4 Marie A. Onyamboko,14 Hugh Reyburn,12 Tharisara Sakulthaew,4 Kamolrat Silamut,4 Antoinette K. Tshefu,14 Noella Umulisa,9 Samwel Gesase,8 Nicholas P. J. Day,4 Nicholas J. White,4 and Arjen M. Dondorp4

1Department of Global Health, Menzies School of Health Research, Casuarina, Northern Territory, Australia; 2Royal Victoria Teaching Hospital, and 3MRC laboratories, Banjul, The Gambia; 4Mahidol Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; 5University of Ilorin Teaching Hospital, Nigeria; 6Komfo Anokye Teaching Hospital, Kumasi, Ghana; 7Hospital Central da Beira, Mozambique; 8Magunga District Hospital, NIMR-Korogwe Research Laboratory, Tanzania; 9Rwamagana Hospital and Nyanza Hospital, Rwanda; 10Kilifi District General Hospital, Kenya; 11Teule District Hospital, Muheza, Tanzania; 12Department of Infectious and Tropical Diseases, London School of Tropical Medicine and Hygiene, United Kingdom; 13Mbarara Teaching Hospital, Uganda; and 14Kingasani Health Centre, Kinshasa, Democratic Republic of the Congo
Correlates with poor outcome

Figure 2: Combinations of presentations and the associated mortality in children in the AQUAMAT trial. Venn diagram illustrating the combinations of presentations and associated mortality from von Seidlein et al. 2012 [31].
Improvements in outcome?
Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 30, 2011 VOL. 364 NO. 26

Mortality after Fluid Bolus in African Children with Severe Infection

Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial


Summary
Primary Outcome: In-Hospital Mortality

- Quinine 297/2713 (11.0%)  \( p=0.002 \)
- Artesunate 230/2712 (8.5%)

Relative difference **22.5%**
(95%CI: 8.1% to 36.9%)
Estimate of effect: AQUAMAT

Concluding sentence:

‘If 4 million African children with severe malaria every year were to receive prompt treatment with parenteral artesunate instead of quinine, and the benefits were similar to those recorded in this trial, then approximately 100 000 lives might be saved per year.’
Mortality after Fluid Bolus in African Children with Severe Infection

Primary endpoint: 48 hour mortality

- Albumin bolus: 10.5%
- Saline bolus: 7.3%
- No bolus
2013: Fluid Boluses continue to be recommended in WHO guidelines
Annual excess mortality of boluses predicted per 1 million doses

<table>
<thead>
<tr>
<th>Definition of shock</th>
<th>Mortality among FEAST participants (%)</th>
<th>Absolute risk difference (95% CI)</th>
<th>Estimated annual No of excess deaths in sub-Saharan Africa if boluses given*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEAST inclusion criteria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>297/3141 (10)</td>
<td>221/2097 (11)</td>
<td>76/1044 (7)</td>
</tr>
<tr>
<td>With malaria</td>
<td>144/1795 (8)</td>
<td>110/1202 (9)</td>
<td>34/593 (6)</td>
</tr>
<tr>
<td>Without malaria</td>
<td>146/1330 (11)</td>
<td>108/884 (12)</td>
<td>38/446 (9)</td>
</tr>
<tr>
<td><strong>WHO Emergency Triage Assessment and Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>27/65 (42)</td>
<td>24/50 (48)</td>
<td>3/15 (20)</td>
</tr>
<tr>
<td>With malaria</td>
<td>14/41 (34)</td>
<td>12/32 (37)</td>
<td>2/9 (22)</td>
</tr>
<tr>
<td>Without malaria</td>
<td>11/22 (50)</td>
<td>11/17 (65)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td><strong>American College of Critical Care Medicine cold shock (with two signs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>189/1733 (11)</td>
<td>147/1196 (12.3)</td>
<td>42/537 (8)</td>
</tr>
<tr>
<td>With malaria</td>
<td>95/1087 (9)</td>
<td>76/753 (10)</td>
<td>19/334 (6)</td>
</tr>
<tr>
<td>Without malaria</td>
<td>92/637 (14)</td>
<td>70/435 (16)</td>
<td>22/202 (11)</td>
</tr>
<tr>
<td><strong>Paediatric Advanced Life Support (2010) compensated shock</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>218/1650 (13)</td>
<td>161/1113 (15)</td>
<td>57/537 (11)</td>
</tr>
<tr>
<td>With malaria</td>
<td>107/1009 (11)</td>
<td>80/684 (12)</td>
<td>27/325 (8)</td>
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5, 200-132, 000 excess deaths/year for 4 million fluid boluses in children with severe malaria whilst WHO continue to recommend boluses.
Malaria and its consequences: direct and indirect burden on health services
Malaria and its consequences

- In 2013 malaria was directly responsible ~ 600,000 deaths in African children
- Areas with highest burdens, have shown little change in disease burdens
- For those hospitalised severe malaria mortality ~10%
- Severe malaria complicated by bacterial infection – 25% case fatality
- **Bacterial co-infection accounts for one third of all malaria deaths**
Malaria and its consequences

1/ Bacterial Co-infection

Invasive bacterial co-infection in African children with Plasmodium falciparum malaria: a systematic review

James Church\textsuperscript{1,2,3} and Kathryn Maitland\textsuperscript{1,2*}
Co-infection bacteraemia % organisms types

Slide and RDT neg, n=143/944
RDT Pos, Slide neg, n=98/501
1-4,999, n=34/405
5,000-50,000, n=34/917
>50,000, n=32/874

nts str.pn
h.inf s.typh
Other gm neg Other gm pos

Non-malaria Recent malaria Malaria infection with low to high parasite burden

Nadjim et al BMJ 2010
Antibiotics - which and who?

- At least 10% children with severe malaria have invasive bacterial infection; case fatality ~ 24%
- Evidence suggests enteric gram negatives esp non-typhoidal Salmonellae
- Paucity of data informing on the dose, length of treatment and antibiotic choice in severe malaria
- Which children to target?
Endotoxaemia is common in children with *Plasmodium falciparum* malaria

- Endotoxaemia (>=0.4 EAA unit) ~27% children
- with severe malaria
- Associated with depressed immune response

**Endotoxin** - marker of gut barrier dysfunction? Targeting antibiotic treatment?
2/ Severe anaemia in sub Saharan Africa

• Is a:
  – leading cause of hospital admission
  – major cause of direct mortality
  – key factor in the 800,000 malaria deaths/year

• Outcome is poor with:
  – high rates of in-hospital (9-10%)
  – Repeated transfusion is required in 25% of children
  – and 6-month (12%) case fatality in survivors,
  – relapse or re-hospitalisation (6%)
WHO Terminology

**Severe anaemia (SA)** Hb < 5-6 g/dl*

**Profound anaemia:** Hb < 4 g/dl

**Severe and complicated anaemia:**
SA plus life threatening features
Pattern of usage of blood: demand

UK
- Largely elective-use
- Pre-planned and predictable

Africa
- ¾’s blood use: paediatric & pregnancy-related
- Largely emergency use
- Unpredictable
- Highly seasonal
WHO needs transfusion?

WHO Transfusion thresholds

Stable

‘Complicated’

Brabin et al 2001: Review of evidence: Haemoglobin and relative risk of death: need for a trial
Meremikwu, M et al 2000 Cochrane review: need for a trial
TRAI NUNG AND TRATMENT OF SEVERE ANAEMIA IN AFRICAN CHILDREN TRIAL
ISRCTN84086586

Factorial design:
3950 children with severe anaemia
• Transfusion strategies
• Long-term management

Uganda

Blantyre
Malawi
Severe malaria research agenda
Adjunctive therapies in severe malaria

• 33 human trials- supportive therapies
• > 60% involving children
• 15 in sub group with cerebral malaria
• Majority single-centre Phase I or II trials
• Early termination for harm- number of trials
• Promising results from early phase trials not reproduced in larger trials (Phenobarbitone, FEAST)
• None have shown benefit
Evidence review: supportive Therapies

- Steroids (Brain swelling x 2)
- Osmotherapies (Mannitol x 2)
- Anti-inflammatory (Pentoxyfilline x 5; aspirin)
- Anti-sequestration (Levamisole)
- Seizure prophylaxis (Phenobarbitone x 3, Fosphenytoin)
- Iron Chelation x 3
- Acidosis Correction (N-acetyl cysteine x 3, L-arginine)
- Fluid and inotrope therapies for shock (x 7)
- Transfusion (x 2)
Murine models: clinical evaluation

The murine cerebral malaria phenomenon

Nicholas J. White\textsuperscript{1,2}, Gareth D.H. Turner\textsuperscript{3}, Isabelle M. Medana\textsuperscript{3}, Arjen M. Dondorp\textsuperscript{1,2} and Nicholas P.J. Day\textsuperscript{1,2}

\textsuperscript{1} Mahidol Oxford Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
\textsuperscript{2} Centre for Tropical Medicine, Churchill Hospital, Oxford, UK
\textsuperscript{3} Malaria Research Group, Nuffield Department of Clinical and Laboratory Sciences, John Radcliffe, Hospital, Oxford, UK

- Of 48 adjunctive interventions evaluated
- 44 (92\%) were successful- often huge benifits
- Only 2 have resulted in trials in human malaria (erthropoietin and activated charcoal)
## Targets for intervention?

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Hypoglycaemia?

Admission glucose mg/dl

3mmols/dl

2.2mmols/dl (~40)

Admission glucose mg/dl

Von-Siedleìn CID 2012
FEAST trial:
Uraemia data in children with malaria

1161 cases with malaria had baseline BUN value
✓ 261/1161 (22%) had BUN $\geq 20$ mg/dL
✓ 65/261 (25%) died within 28 days
➢ 58% of malaria deaths had a high BUN

Deaths and level of renal function (by BUN) in those with malaria

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<th>BUN $\geq 20$ mg/dL</th>
<th>Total</th>
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<tr>
<td>Alive</td>
<td>852</td>
<td>196</td>
<td>1048</td>
</tr>
<tr>
<td>Deaths</td>
<td>48 (5%)</td>
<td>65 (25%)</td>
<td>113 (10%)</td>
</tr>
<tr>
<td>Total</td>
<td>900</td>
<td>261</td>
<td>1161</td>
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Timing of the deaths of in hours from randomisation for those with malaria with BUN\(\geq 20\text{mg/dl}\)

<table>
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<tr>
<th>Period</th>
<th>&lt;8 hours</th>
<th>8-&lt;24 hrs</th>
<th>24-&lt;48 hrs</th>
<th>48 hrs – 28 days</th>
<th>Total</th>
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<td>Distribution of deaths over time</td>
<td>26</td>
<td>20</td>
<td>10</td>
<td>9</td>
<td>65</td>
</tr>
<tr>
<td>Percentage of those that died with BUN(\geq 20\text{mg/dl})</td>
<td>40%</td>
<td>31%</td>
<td>15%</td>
<td>15%</td>
<td>100%</td>
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Similar to overall results in FEAST:
70% of deaths in this subgroup occurred before 24 hours
Small proportion died after 48 hours
(BUN not repeated /urine output not measured)
We need to do more trials.....
Going forward........

- Cost of interventions remained relatively static or decreased over time
- Cost of doing clinical trials - increased vastly
- Time from grant submission to first patient enrollment ~ 2-3 years (TRACT 2011; Sept 2014)
- Closure of trial – disbanding of TMG & trial teams
- Current model/ landscape for research: one or two trials on continent