Determinants of Malaria

Parasite  Environment  Vector

Host
Malaria Treatment!
Rationale for drug & dosage

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Reasons for changes of Malaria Burden

- Population growth and movements
- Changes in environment breeding sites
- Drug resistance
- Changes in diagnostic habits, recording
- Climate changes?
- Lack of understanding of the pathogen
I am growing into a big problem
Implications for the public sector.

What do you mean it’s a whole new ball game?
## Total Financial requirements for providers and consumers over 5 year plan

<table>
<thead>
<tr>
<th></th>
<th>Year 1 2004 Paeds</th>
<th>Year 2 2005</th>
<th>Year 2006</th>
<th>Year 4 2007</th>
<th>Year 5 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GoK</strong></td>
<td>3.150 M$</td>
<td>18.462 M$</td>
<td>18.462 M$</td>
<td>18.462 M$</td>
<td>18.462 M$</td>
</tr>
<tr>
<td><strong>Mission / NGO</strong></td>
<td>1.241 M$</td>
<td>7.0382 M$</td>
<td>7.038 M$</td>
<td>7.038 M$</td>
<td>7.038 M$</td>
</tr>
<tr>
<td><strong>Private</strong></td>
<td></td>
<td></td>
<td>15.899 M$</td>
<td>15.899 M$</td>
<td>15.899 M$</td>
</tr>
<tr>
<td><strong>Retail sector</strong></td>
<td></td>
<td></td>
<td></td>
<td>29.404 M$</td>
<td>29.404 M$</td>
</tr>
<tr>
<td><strong>Total donor or GFATM request</strong></td>
<td>4.523 M$</td>
<td>26.228 M$</td>
<td>26.228 M$</td>
<td>26.228 M$</td>
<td>26.228 M$</td>
</tr>
</tbody>
</table>

* Includes WHO 3% handling charges
Age-distribution of treatment costs

- < 1 yr, 5%
- 1-4 yrs, 18%
- 5-14 yrs, 20%
- 15+ yrs, 57%
Percentage of clients treated appropriately at baseline and final data collection

- **All patients**
  - Baseline: 34%
  - Final: 61%

- **Bondo/Siaya**
  - Baseline: 38%
  - Final: 59%

- **Kericho**
  - Baseline: 32%
  - Final: 63%

N=990, N=436, N=554, N=741, N=465, N=276
Diagnosis

- High index of suspicion
- Blood slide remains the gold standard
- Immunofluorescence techniques
- Antigen capture techniques
- Enzyme detection techniques
- PCR technique
- Clinical
- Presumptive
Assumptions

- Appropriate technique used by a qualified personnel used to make the diagnosis

- The species being treated is the right one

- There is some good understanding of disease epidemiology
Do we believe!

- Fever and malaria are not synonyms
- IMCI guidelines are resource for deficient settings rather than the norm
- Very few things resemble malaria except malaria itself
- In non-severe malaria the problem is the parasite
- In severe disease the imminent cause of death is the deranged homeostasis or end organ failure
- Saying no requires more insight than yes
Malaria & Fever

- **Kombewa**
  - Study 1 of 3152 febrile children 43% malaria positive
  - Study 2 of 252 febrile children only 95 (38%) malaria positive

- **Siaya**
  - 60% of people with negative test get treated

- **EIR (starting at 100 – 300 b/p/y)**
  - Asembo with 95% ITN coverage – 7 b/p/y
  - Komewa with 70% ITN coverage – 13 b/p/y
Disease pathogenesis

- Poorly understood

- Continuum spectrum
  - Asymptomatic → Coma

- Broad classification
  - Uncomplicated malaria
  - Complicated or severe malaria

- Severe Malaria
  - Severe malaria, respiratory distress, CM
Ears of the hippopotamus
Choice of Drugs

- Efficacious and effective
- Meets public health requirements
- Availability
A good drug?

Effective drug present in the body for long enough

No. of parasites in the body

Days after treatment

Level detectable by lab

0 2 7 14 28
Determinant of treatment policy

- Parasite life cycle
- Drug Kinetics
- UTL
- Drug sensitivity pattern
- Affordability
- Political will
- Health infrastructure
Aims of treatment

- Radical clearance of parasites
  - Aim for 3 – 5 life cycles
- Prevent severe disease
- Prevent clinical and parasitological failures
- Prevent public health treatment failures
- Improve wellbeing
  - Choice of drugs
  - Supportive care
<table>
<thead>
<tr>
<th>Prognostic Value</th>
<th>Clinical manifestations or Laboratory findings</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children Adults</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+               ?</td>
<td>Prostration</td>
<td>+++</td>
</tr>
<tr>
<td>+++             ++</td>
<td>Impaired consciousness</td>
<td>+++</td>
</tr>
<tr>
<td>+++             +++</td>
<td>Respiratory distress (acidotic br)</td>
<td>+++</td>
</tr>
<tr>
<td>+               ++</td>
<td>Multiple convulsions</td>
<td>+++</td>
</tr>
<tr>
<td>+++             +++</td>
<td>Circulatory collapse</td>
<td>+</td>
</tr>
<tr>
<td>+++             +++</td>
<td>Pulmonary oedema</td>
<td>+/-</td>
</tr>
<tr>
<td>+++             ++</td>
<td>Abnormal bleeding</td>
<td>+/-</td>
</tr>
<tr>
<td>++              +</td>
<td>Jaundice</td>
<td>+</td>
</tr>
<tr>
<td>+               +</td>
<td>Haemoglobinuria</td>
<td>+/-</td>
</tr>
<tr>
<td>+               +</td>
<td>Severe anaemia</td>
<td>+++</td>
</tr>
</tbody>
</table>

On scale from + to +++; +/- indicates infrequent occurrence
? Data not available
Treatment regimen

Combination therapy
  – ACT
    Co-formulated
      – CPDs pharmacologically compatible
Treatment success?

<table>
<thead>
<tr>
<th>Days after treatment</th>
<th>Level detectable by lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Immediate / early failure</td>
</tr>
<tr>
<td>7</td>
<td>Successful treatment</td>
</tr>
<tr>
<td>14</td>
<td>Late failure</td>
</tr>
</tbody>
</table>

Graph showing the number of parasites in the body over days after treatment.
Effective treatment – combination therapy?

No. of parasites in the body

Days after treatment

Drug that acts rapidly to reduce parasitaemia

Effective drug present in the body for long enough
Effective treatment – combination therapy?

Usually one fast-acting drug plus one drug that lasts longer so days of treatment few.

Chance of resistance developing to two drugs at the same time much smaller.
Good oral therapy?

- Simple dosing – better compliance
  - Preference od > bd > tds
  - Short duration, prefer 1 day > 2 days > 3 days etc

- Preparation easy to take (taste, liquid / tablet)

- Works!

- Safe

- Prevents rapid development of resistance
Artemisinin-based combination therapies (ACTs)

- ACTs currently recommended by WHO
- Drug combinations, particularly ACTs, have the potential to improve efficacy and delay the development and selection of drug-resistant parasites
- Countries that need to replace SP or AQ as first-line treatment for malaria need to move to ACT
- Options:
  - Artemether–lumefantrine (only fixed combination* - viable option) (paediatric formulation phase III study completed)
  - Artesunate plus amodiaquine (loose combination)
  - Chlorproguanil-dapsone plus artesunate (phase III ongoing)
  - Dihydro-artemisinin-piperaquine (phase III completed)
  - Artesunate-Mefloquine (Limited data in Africa)
  - Pyronaridine/Artesunate (phase III to start)
Formulation & Artemisinins

- Unstable in solution
- If in solution has to be in an alkaline medium
- Short shelf life (2 years)
- Powder highly hygroscopic
- Artemether (lipid soluble)
- Artesunate (water soluble)
- Suspensions no good data available
- Do we really need suspensions of dispersible tablets?
Recommended Treatment
Uncomplicated malaria

- Non Pregnant
  - Artemether/Lumefantrine
  - Quinine 2\textsuperscript{nd} line (not ideal)

- Pregnant (dilemmas)
  - 1\textsuperscript{st} trimester – Quinine
  - 2\textsuperscript{nd} & 3\textsuperscript{rd} trimester – Artemether/Lumefantrine

- Prophylaxis
  - Malarone, Mefloquine, Doxycyline
  - Standby treatment pack
Antimalarial Treatment Severe Malaria

Non pregnant
- Artesunate (ART) + ACT first line treatment
- Artemether (ARTM) + ACT first line treatment
- Quinine (QN) + ACT first line

Pregnant
- 1st trimester QN – 7days
- 2nd trimester as non pregnant

?QN + Doxycycline / QN + Clindamycin
?ART/ARTM + Doxycycline / ART + Clindamycin
?QN for 7 days
?ART/ARTM for 7 days
Vivax or Ovale

- Chloroquine 10 mg base/kg then 5 mg base/kg 6, 24, 48 hrs

&

- Primaquine 0.5 mg base/kg OD X 14 days

- If CQ resistant use quinine

or

- Mefloquine 13.7 mg base/kg start the 6-12 hrs 9.1 mg base/kg + Primaquine as above
Prophylaxis

- Proguanil
- Doxycycline
- Atovaquone/proguanil
- Mefloquine

Standby treatment kit
Drug Development

- Effort directed towards short half life
- Prophylaxis drugs very few in the pipeline
- More effort on combination after phase IIb
- Recycling of drugs
- How many CTs can the market handle
- Products awaiting sponsors
- Competing interventions
Malaria MX commandments

- HDU or ICU management protocol
- Appropriate & Effective Antimalarials
- Fluids
- Glucose
- Safe Blood
- Anticonvulsants
- Monitoring
- Parental counseling
- Follow up
Guiding principles

- Data is inadequate
- Despite the great knowledge of the disease no impact on mortality
- Vaccine still beyond the horizon
- Drugs alone will not reduce mortality
- Supportive care in severe malaria
- Drug resistance is inevitable
- Exploiting the malaria and anopheles genome
- Long half-life of antimalarials?