Understanding and Improving the Case Management of Children with Severe Malaria in DR Congo, Nigeria and Uganda: Results of the CARAMAL study – Community Access to Rectal Artesunate for Malaria

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Makerere University School of Public Health, Uganda

RBM Kigali, 28th June 2022
Severe malaria – a medical emergency

627,000 deaths, mainly African children, 80% in 15 countries

Parenteral artemisinin-based combination therapy (ACT)

WHO 2021
Severe malaria – a medical emergency

627,000 deaths, mainly African children, 80% in 15 countries

Parenteral artemisunate/artemether/quinine for min. 24 hours (IM or IV) + full course of oral artemisinin-based combination therapy (ACT)

Where IM injections of artesunate are not available, treat children < 6 years with a single rectal dose of artesunate (10 mg/kg bodyweight), and refer immediately to an appropriate facility for further care.
Pre-referral rectal artesunate: prior evidence

1. In a multi-country randomised controlled trial in the mid-1990s, pre-referral RAS reduced case fatality rate in children <6 years with signs of severe malaria by 26% (short referral) to 51% (if referral took more than 6 hours) (Gomes 2009)

   Context: CFR (Tanzania/Ghana) 4%, >90% referral completion, no data on post-referral care, but assumed to be good.

2. Pre-referral RAS in combination with strengthened referral and post-referral treatment reduced massively (over 90%) severe malaria CFR in one district in Zambia (Green 2019).

   Context: Emergency transport system, no drug stock-outs, full health care worker training and high motivation ("ideal" conditions)

Both studies represent introduction of RAS in optimized conditions

1. What is the optimal way of rolling out RAS on a large (national) scale?
2. What is the effect of RAS implemented without major supportive interventions?

Effectiveness vs Efficacy
CARAMAL: A 3-year operational research project (2018-2020) funded by UNITAID

Goal

Contribute to reducing malaria mortality in children by improving the community management of cases of suspected severe malaria

Research questions

• What are minimal health system requirements for RAS to be effective as part of the continuum of care, from the community to a referral facility?
• What are unintended consequences of RAS implementation at all levels of care?
• Can the introduction of pre-referral RAS reduce severe malaria case fatality ratio under real-world operational circumstances?
• What are costs and cost-effectiveness of scaling up RAS?
# CARAMAL Population Coverage


<table>
<thead>
<tr>
<th>Project area</th>
<th>DR Congo</th>
<th>Nigeria</th>
<th>Uganda</th>
<th>Total</th>
<th>PSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenge, Kingandu and Ipamu Health Zones</td>
<td>Kenge, Kingandu and Ipamu Health Zones</td>
<td>Adamawa State, Fufere, Mayo-Belwa, Song LGAs</td>
<td>Apac, Kole and Oyam Districts</td>
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<tr>
<td><strong>Population</strong></td>
<td>785,967</td>
<td>746,949</td>
<td>995,986</td>
<td>2,528,902</td>
<td></td>
</tr>
<tr>
<td>&lt; 5 years</td>
<td>268,197</td>
<td>130,430</td>
<td>200,518</td>
<td>476,054</td>
<td>13,758 (3% of all U5 in 2 years)</td>
</tr>
</tbody>
</table>
CARAMAL operational research activities
Lengeler / Burri et al. medRxiv 2021, doi.org/10.1101/2021.12.10.21266567

Health Provider Survey
Household Survey
Patient Surveillance System (PSS)

~10 months
~15 months

Pre
Post

Drug resistance

RAS roll-out

Cost

Drug resistance

2018
May
June
July
August
September
October
November
December
2019
February
March
April
May
June
July
August
September
October
November
December
2020
February
March
April
May
June
July
August
CARAMAL patient enrolment and follow-up

- **Initial treatment seeking**
- **RAS administration & referral advise**
- **Referral completion**
- **Post-referral treatment: inj. AS + ACT**
- **Health outcome**

**Total number of severely ill children in study: 13,758**

- Enrolment of children <5 years with fever, danger signs & positive mRDT

- Day 28 household follow-up
  - **health status**
  - Hb, mRDT
  - treatment seeking
Beyond the primary scope of this CARAMAL Child is healthy infected mild symptoms severe symptoms

CARAMAL PSS study population

- Children <5 years with fever, a positive malaria test (RDT) & danger signs
- With Day 28 home visit completed
- Pre-RAS (10 months) ≈ 1/3  Post-RAS (15 months) ≈ 2/3

<table>
<thead>
<tr>
<th></th>
<th>DR Congo</th>
<th></th>
<th>Nigeria</th>
<th></th>
<th>Uganda</th>
<th></th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-RAS</td>
<td>Post-RAS</td>
<td>Pre-RAS</td>
<td>Post-RAS</td>
<td>Pre-RAS</td>
<td>Post-RAS</td>
<td></td>
</tr>
<tr>
<td>Community health</td>
<td>60</td>
<td>104</td>
<td>178</td>
<td>180</td>
<td>1,608</td>
<td>2,285</td>
<td>4,415</td>
</tr>
<tr>
<td>workers (CHW)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Primary health</td>
<td>701</td>
<td>2,177</td>
<td>67</td>
<td>233</td>
<td>1</td>
<td>33</td>
<td>3,212</td>
</tr>
<tr>
<td>centres (PHC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Referral health</td>
<td>973</td>
<td>1,525</td>
<td>351</td>
<td>496</td>
<td>620</td>
<td>2,166</td>
<td>6,131</td>
</tr>
<tr>
<td>facilities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1,734</td>
<td>3,806</td>
<td>596</td>
<td>909</td>
<td>2,229</td>
<td>4,484</td>
<td>13,758</td>
</tr>
</tbody>
</table>
In the field, DR Congo

Training of field workers, DR Congo

Supervision visit, Uganda
Study enrolment (bars) & RAS use (line)
 ✓ In all countries, referral completion to a Referral Health Facility was slightly lower among RAS users compared to RAS non-users.

 ✓ If the use of RAS reduces referral rates, this compromises treatment and hence the survival of the children.
Referral health facility treatment

- Referral Health Facility data was analysed for 7,983 children.
- Use of injectable antimalarials was very high in all three countries (> 95%).
- A full course of an ACTs was often given in DR Congo (78.7%).
- In Uganda and Nigeria, providers were mostly given a prescription instead of the treatment, resulting in moderate levels of ACT treatment in Uganda (45.7%) and very low levels in Nigeria (1.7%).
- As a consequence, a full course of treatment at the health facility (parenteral antimalarial and an ACT) was frequent in DR Congo (76.2%), moderate in Uganda (44.7%) and low in Nigeria (1.2%).

Not completing the full course of an ACT is leading:
(1) to incomplete cure
(2) to monotherapy - implying a higher risk of resistance development
In total 223 deaths were registered in the PSS.

The CFR was 6.7% (135/2011) in DRC, 11.7% (69/589) in Nigeria, and only 0.5% (19/3686) in Uganda (p < 0.001).

Note difference in y-axis scales.

Usually death occurred in the days immediately after enrolment.

Mortality was higher in the RAS group, in Nigeria and marginally so in DRC.
Day 28 health status
Hetzel et al., medRxiv 2021.09.24.21263966

✓ Of 6020 patients tested by mRDT (HRP2/pLDH Combo tests) at D28 follow-up, 44.0% were still positive in DRC, 50.2% in Nigeria, and 69.5% in Uganda. Most positive results likely due to remaining circulating antigen

✓ A substantial percentage of children were either still sick or deceased at Day 28: 19% in DRC, 17% in Nigeria, and 16% in Uganda

✓ This shows that patient management for severe illness cases is inadequate
Of 2211 children included in the analysis, 96% visited a second provider after attending a CHW.

The majority of CHWs recommended caregivers to take their child to a designated RHF (65%); however, only 59% followed this recommendation.

Many children were brought to a private clinic (33%), even though CHWs rarely recommended this type of provider (3%).

Children who were brought to a private clinic were more likely to receive an injection than children brought to a RHF (78% vs 51%, p<0.001).

Children who only went to non-RHF providers were less likely to receive an artemisinin-based combination therapy (ACT): \( OR = 0.64, 95\% CI 0.51–0.79 \)
Lessons learned: Post-referral case management

<table>
<thead>
<tr>
<th>Observations</th>
<th>Learnings and Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Many children did not receive an ACT after RAS (+/- inj AS) – resulting in monotherapy treatment with low cure rate</td>
<td>• Ensure full course of ACT is dispensed at referral facility (with at least first dose taken at facility)</td>
</tr>
<tr>
<td>• ACT was often provided as prescription only, expecting caregivers to purchase the medicine after discharge</td>
<td>• Strengthen supply</td>
</tr>
<tr>
<td></td>
<td>• Training of caregivers</td>
</tr>
<tr>
<td></td>
<td>• Enforce free/low cost treatment at facilities</td>
</tr>
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<td></td>
<td>• M&amp;E for tracking treatment quality</td>
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Main conclusions

• In the CARAMAL countries, RAS - an efficacious medicine - was introduced in areas with weak health systems and impoverished communities; multiple severe system deficiencies were observed - leading to low cure rates and high case fatality rates.

• RAS is part of the continuum of care for severe malaria. Without considering the health system as a whole (including treatment seeking patterns, supplies of multiple commodities, referrals and supervision) reducing case fatality from severe malaria and other major childhood diseases is unlikely to be achieved.
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## Lessons learned: Treatment seeking

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<tr>
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<tr>
<td>• Important role of chemists/drug shops (NG) and private clinics (UG)</td>
<td>• Private sector should be recognised as important stakeholder and equipped to provide adequate care and/or advice</td>
</tr>
<tr>
<td></td>
<td>• Consider RAS pre-referral treatment by private providers (e.g. accredited drug stores)</td>
</tr>
<tr>
<td>• CHWs are often not the first source of care for cases of severe malaria</td>
<td>• Ensure CHWs are skilled, trusted, and recognised as first points of care <em>particularly where health facilities are harder to reach</em></td>
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<tr>
<td></td>
<td>• Strengthen supply chain to ensure that commodities are available at all times (<em>the right drug at the right time in the right place</em>)</td>
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Lessons learned: Treatment at community level (CHW and PHC)

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<tr>
<td>• Acceptance of RAS is good and use is high when product is available</td>
<td>• Ensure functioning supply chain and sufficient stock per provider – which needs to be balanced against relatively short shelf-life</td>
</tr>
<tr>
<td>• RAS is frequently under-dosed in children ≥3 years of age (one rather than two suppositories)</td>
<td>• Functional and sustainable commodity tracking system and easy access to re-supply</td>
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<tr>
<td>• Big differences between individual providers in number of patients treated with RAS – making the supply chain more difficult to manage</td>
<td>• Need for regular supervision (can be effectively a way of re-supplying RAS)</td>
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Lessons learned: Referral

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<tbody>
<tr>
<td>• Referral from CHW to PHC rather than to designated referral facility</td>
<td>• Patients should be referred directly to a facility that can offer adequate post-referral treatment (in the case of severe malaria usually secondary/tertiary facilities).</td>
</tr>
<tr>
<td>(may delay/prevent full treatment)</td>
<td>• Subsidized emergency transport or social health insurance to support completion of referral</td>
</tr>
<tr>
<td>• Referral completion from CHW to referral facility often low (&lt;60%)</td>
<td>• Need “back-up plan” for children who don’t complete referral to prevent deterioration and mono-therapy/incomplete cure (for example, ensure full-course ACT administration)</td>
</tr>
<tr>
<td>• Referral less likely in patients treated with RAS; anecdotal evidence that</td>
<td>(Real-world scenario not considered in current recommendations)</td>
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<tr>
<td>children’s condition improves quickly after RAS, diminishing perceived need</td>
<td></td>
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<tr>
<td>for referral</td>
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Lessons learned: Sustained financing

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<td>• iCCM platforms are sustained by various donors (no one donor financing all the pieces); hence piecemeal approach leading to multiple stockouts (<em>a chain is only as strong as its weakest link</em>)</td>
<td>• Concerted action plan by the MOH to ensure all components of the essential continuum of care for childhood diseases are available at all times</td>
</tr>
<tr>
<td>• “Health systems strengthening” is a donor orphan, being generally considered to be for “domestic investments” - which are usually stretched thin</td>
<td>• Progressive take over by domestic financing could ensure more continuity</td>
</tr>
<tr>
<td></td>
<td>• Progressive sensitization and inclusion of the private sector in the provision of proper care</td>
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