Community Access to Rectal Artesunate for MAlaria (CARAMAL)

Addressing the burden of malaria deaths by optimizing the use of rectal artesunate
What is severe malaria?

According to WHO (3rd edition malaria guidelines):
Severe falciparum malaria: one or more of the following, occurring in the absence of an identified alternative cause and in the presence of P. falciparum asexual parasitaemia

- Impaired consciousness
- Prostration
- Multiple convulsions
- Hypoglycaemia
- Severe malaria anaemia
- Renal impairment
- Jaundice
- Pulmonary oedema
- Significant bleeding
- Shock
- Acidosis
- Hyperparasitaemia >10%

iCCM: Integrated Community Case Management is an equity-focused strategy that complements and extends the reach of public health services by providing timely and effective treatment of malaria, pneumonia and diarrhoea to populations with limited access to facility-based health care providers, and especially to children under 5 (WHO)

According to iCCM: Children with one or more danger sign: cough for 14 days or more, diarrhoea for 14 days or more, diarrhoea for 14 days or more, blood in stool, fever for last 7 days or more, convulsions, not able to drink or eat anything, vomits everything, has HIV and any other illness, or unusually sleepy or unconscious (Caring for Sick Child in the Community 2014)

According to National Guidelines (i.e., DRC): Severe malaria is defined at community level-as danger signs + fever
The burden of malaria

**445,000 malaria deaths in 2016**

- The majority of malaria inpatient deaths are in West, Central, and East Africa
- 80% in 15 countries
- DRC, Nigeria, Uganda: **173,000** deaths
How do you treat severe malaria?

The WHO Guidelines for the Treatment of Malaria 3rd Edition strongly recommends injectable artesunate for treatment of severe malaria.

**Treating severe malaria**

Treat adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) with intravenous or intramuscular artesunate for at least 24 h and until they can tolerate oral medication. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of an ACT (add single dose primaquine in areas of low transmission).

*Strong recommendation, high-quality evidence*

**Revised dose recommendation for parenteral artesunate in young children**

Children weighing < 20 kg should receive a higher dose of artesunate (3 mg/kg bw per dose) than larger children and adults (2.4 mg/kg bw per dose) to ensure equivalent exposure to the drug.

*Strong recommendation based on pharmacokinetic modelling*

**Parenteral alternatives when artesunate is not available**

If parenteral artesunate is not available, use artemether in preference to quinine for treating children and adults with severe malaria.

*Conditional recommendation, low-quality evidence*
If Injectable artesunate is not readily available...

- Rectal artesunate (RAS) is recommended by WHO for pre-referral treatment of children under six with severe malaria danger signs
- RAS rapidly (within 24 hours) clears 90% or more of malaria parasites
- In children younger than six years of age who cannot reach a facility in less than six hours, RAS can reduce the risk of death or permanent disability by up to 50%

- RAS, however, is not complete treatment; linkages must exist between communities and facilities that facilitate smooth, timely completion of referral to a well-equipped and capable health system for treatment with injectable artesunate and a full course of ACTs
In patients < 6 years of age not in clinic after more than 6 h, half were still not there after more than 15 h.

In these patients, pre-referral rectal artesunate significantly reduced death or permanent disability.

29/1566 [1.9%] vs 57/1519 [3.8%], risk ratio 0.49 [95% CI 0.32–0.77]
What are the requirements for effective and complete severe malaria case management?

1. Recognition of potential malaria infection and the need to seek care in a timely fashion by the child’s caregiver

2. Recognition of the illness and its severity by the CHW or primary care provider

3. Appropriate administration of QA RAS

4. Referral to a sufficiently equipped, higher-level health facility able to manage the sick child with parenteral treatment

5. Completion of the referral by the caregiver

6. Proper severe malaria case management at the higher-level health facility

**Recognize the Danger Signs**
A febrile child or a child with recent history of fever with one or more danger signs:
- Unconscious or Lethargic
- Not able to drink or eat
- Vomits everything
- Seizing or Convulsing

**Transfer Urgently**
The child must be referred immediately to the nearest hospital or health care facility for a full course of antimalarial medicine by IV or IM.

**Administer Rectal Artesunate**
The community health worker prepares the child and administers rectal artesunate.

**Treating Severe Malaria**
- Treat adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) with intravenous or Intramuscular artesunate for at least 24 h and until they can tolerate oral medication. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of ACT.
- Strong recommendation, high-quality evidence

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Community Access to Rectal Artesunate for Malaria (CARAMAL) 2018-2020

- **CARAMAL** introduces rectal artesunate (RAS) at CHW level under real world settings
- CARAMAL will increase access to QA rectal artesunate (RAS) as part of strengthened severe malaria case management systems through increased demand and adoption, thereby reducing severe malaria case fatality rates in children.

- **Project outputs**
  - QA RAS made available
  - RAS introduced as pre-referral treatment
  - Evidence generated and shared on use of RAS
  - Transition to evidence-based and step-wise scale-up

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**Funding agency**

**Project coordination**

**Country Research Partners**

**Operational research**

**Supporting partners**
CARAMAL Operational Research Objectives

**Goal** Contribute to **reducing malaria mortality in children** by improving the community management of suspected severe malaria. Advance the **development of operational guidance** for the scale-up of pre-referral RAS for severe malaria.

**Research questions**

- What are **minimal requirements to ensure that RAS is an effective part of the continuum of care** from the community to a referral facility?
- What are **unintended consequences** of scaled implementation at all levels of care, and how can they be addressed?
- Is there **use of RAS beyond the recommended guidelines**?
- Can the introduction of pre-referral RAS **reduce severe malaria case fatality ratio** over time under real-world operational circumstances?
- What are **costs and cost-effectiveness** of scaling up RAS?
### Project status and preliminary observations

#### INFORMATION GATHERING & DATA GENERATION

- Referral health facility assessments conducted (Q3-Q4 2017)
- RAS landscaping assessment completed
- Patient Surveillance System (PSS) launched and in operation across all three countries
- Household Survey (HHS) and Health Care Provider Survey (HCPS) complete in all three countries
- Artemisinin resistance monitoring ongoing

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### IMPLEMENTATION
- Secured WHO pre-qualification for 100mg RAS products from Cipla and Strides
- Supported RAS quantification exercises and placement of orders in three project countries
- Supportive interventions (mentoring, training) implemented at referral health facilities
- Development of RAS training materials for inclusion in iCCM curricula
- Over 7,000 CHWs trained in administration of RAS across all three countries

### NON-PROJECT COUNTRY ENGAGEMENT
- 53% of African countries (30/56) have included RAS in their National Malaria Treatment Guidelines
- 56% (17/30) of those have recommendations aligned with the latest WHO treatment guidelines
- Light-touch support to non-project countries being pursued through key partners (e.g., PMI, MMV) and ministries directly

### PRELIMINARY OBSERVATIONS
- Capacity of existing iCCM systems to expand to severe malaria CM
- Challenges with referral between community and health system
- Persistent use of quinine for treatment of severe malaria patients
- Treatment seeking in private sector
Questions/Comments?