

WHO Update on Rectal Artesunate for Pre-referral Treatment in Children

12th Annual RBM Case Management Working Group Meeting
Accra, Ghana. 21-25 August 2023



Dr. Peter OLUMESE,
Global Malaria Programme
WHO, Geneva, Switzerland.

Global **Malaria** Programme



**World Health
Organization**

Treatment of Severe malaria – WHO recommendations

- Therapeutic objectives
 - Main objective is to prevent the patient from dying
 - Secondary objectives are to prevent disabilities and prevention of recrudescence infection
- Death from severe malaria often occurs within hours of onset of symptoms or admission to hospital
 - Essential that therapeutic concentrations of a highly effective antimalarial are achieved as soon as possible




5.2.2 Treating severe malaria

5.2.2.1 Artesunate

 Strong recommendation for , High certainty evidence

Treating severe malaria (2015)

Adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) should be treated 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, treatment should be completed with 3 days of an ACT.

 Strong recommendation for

Treating severe malaria in children (2015)

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.

*Not evaluated using the GRADE framework; recommendation based on pharmacokinetic modelling

5.2.2.2 Parenteral alternatives when artesunate is not available

 Conditional recommendation for , Low certainty evidence

Parental alternatives when artesunate is not available (2015)

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



5.2.2.3 Pre-referral treatment options

Strong recommendation for , Moderate certainty evidence

Pre-referral treatment options (2015)

Where complete treatment of severe malaria is not possible, but injections are available, adults and children should be given a single intramuscular dose of artesunate, and referred to an appropriate facility for further care. Where intramuscular artesunate is not available, intramuscular artemether or, if that is not available, intramuscular quinine should be used.

Where intramuscular injection of artesunate is not available, children < 6 years should be treated with a single rectal dose (10mg/kg bw) of artesunate, and referred immediately to an appropriate facility for further care. Rectal artesunate should not be used in older children and adults.



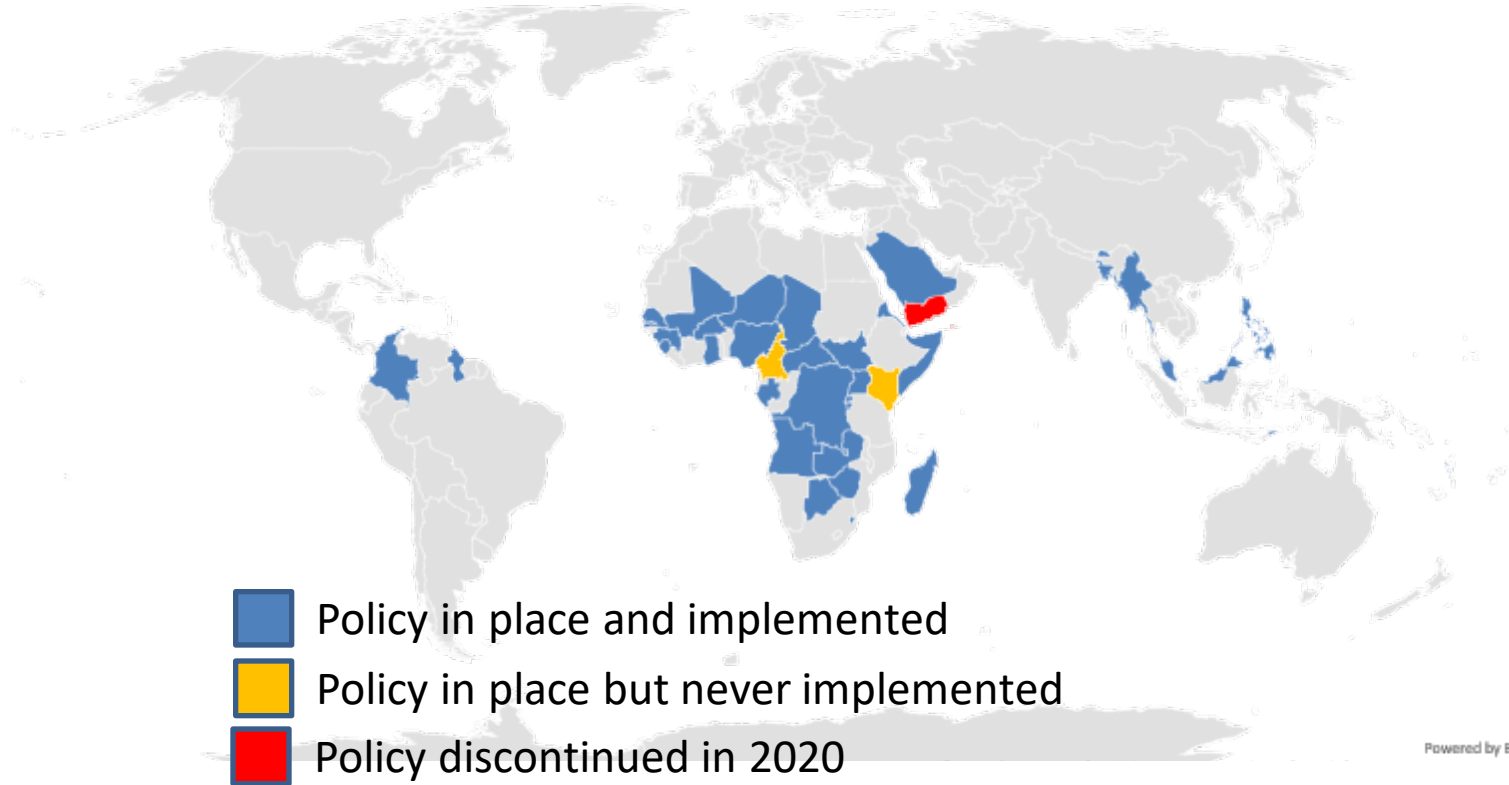
Treatment of Severe malaria (2015)

- Pre-referral treatment – follow on Action
 - Refer the patient as soon as feasible to a centre where full management is available
 - Where referral is not possible after the initial treatment:
 - Insufficient evidence on continued rectal treatment, but recommendation based on expert opinion:
 - Rectal treatment should be continued until the patient can tolerate oral medication, then
 - Administer a complete course of an effective ACT



Country uptake of pre-referral treatment policy

Countries with policy of pre-referral treatment of severe malaria in children in 2020
with quinine, artemether IM or rectal artesunate



- In 2018, RAS became available at a quality-assured standard, with the WHO prequalification of two 100 mg products – a key factor for large-scale procurement of the commodity using multilateral funds.
- Between 2018 and 2020, about 3 million WHO-prequalified suppositories were procured by more than 20 countries.

source: NMCP data submitted to WHO for WMR2021

Effective Implementation

- **The CARAMAL Project:**
 - The purpose of the Community access to rectal artesunate for malaria (CARAMAL) project was to determine if the introduction of quality assured RAS can reduce severe malaria case fatality under prevailing “real-world” operational circumstances. No supportive intervention neither to ensure referral nor post referral treatment was provided. The project was implemented in 3 countries, DRC, Nigeria and Uganda (2017-2020).
 - In April 2021, WHO GMP as part of its role in the UNITAID-funded CARAMAL project convened a Technical Consultation to review the lessons learned.
 - The aim was to evaluate the project based on preliminary unpublished reports and use the lesson learned to develop operational guidance on RAS use as pre-referral treatment of severe malaria in children.
- The same preliminary findings were also presented to the Malaria Policy Advisory Group in October 2021

WHO through an information note made some risk Mitigation recommendations based on MPAG's advice to temporarily limit the use of RAS, with a plan to conduct a formal review of the evidence as stated below:

The WHO Global Malaria Programme, in consultation with other relevant departments, will conduct a formal evidence review and develop detailed guidance on the conditions under which the use of this tool can be implemented safely and effectively. Such guidance will be shared with countries as soon as it becomes available.

- In consultation with relevant departments, convening an independent technical group to undertake a technical review of all publications and study reports (including all CARAMAL -published and on-line unpublished), which have deployed RAS at programmatic level to:
 - Determine the factors required to safely and effectively deploy rectal artesunate as pre-referral treatment for severe malaria in areas where complete treatment for severe malaria is not immediately accessible.

Technical consultation to review the effectiveness of rectal artesunate used as pre-referral treatment of severe malaria in children

Meeting report,
18–19 October 2022



- The outcomes of the technical consultation, form the basis of this 2023 update on the use of RAS as a pre-referral treatment for severe *Plasmodium falciparum* malaria.

The use of rectal artesunate as
a pre-referral treatment for severe
Plasmodium falciparum malaria

2023 update

4 July 2023

<https://www.who.int/publications/i/item/9789240075375>

From Efficacy to Effectiveness

- The technical review identified several issues in the design of the CARAMAL study, which have left it susceptible to a number of biases and made the results difficult to interpret, particularly in terms of the impact of RAS on mortality and referral completion.
 - The CARAMAL project, however, highlighted many challenges and deficiencies along the cascade of care, revealing health system weaknesses and inadequate quality of care.
- Implementation research on scaling up the use of RAS for treatment of severe malaria at the community level in Zambia showed that the CFR decreased from 3.1% to 0.1% in the two high-intensity intervention districts and from 10.7% to 1.4% in the other districts

Artemisinin resistance

- In a sub study in Uganda, the CARAMAL project reported that the prevalence of the kelch 13 (K13) C469Y marker for partial artemisinin resistance increased at day 28 post-RAS in children who failed to complete referral treatment (20%) compared to on day 0 in children directly presenting at a referral health facility, without receiving RAS (6.2%).
 - This finding is difficult to interpret, as it was based on a relatively small number of children and convenience sampling was used.
 - K13 C469Y molecular markers for partial artemisinin resistance were present in Uganda before RAS was deployed and were widely present and increasing in the northern provinces – in some CARAMAL districts and in other districts where RAS was not deployed.
- Despite the limitations noted above, this study provides a signal that RAS alone, when not followed by referral and complete treatment with a full course of ACT, may select partial artemisinin-resistant parasites with the K13 C469Y mutation.

Risk mitigation

- Countries that are already implementing or considering implementation of RAS for pre-referral treatment of severe malaria need:
 - to strengthen all aspects of the continuum of care for a severely sick child – from community health workers being adequately trained and stocked for giving RAS in the areas where it is most needed, to ensuring rapid transfer and access to referral facilities where a complete course of post-referral treatment is given following WHO recommendations for the treatment of severe malaria;
 - to ensure support for adequate supply chain management and referral systems from community health workers and health facilities to referral treatment centres, which is essential for achieving the intended impact of RAS;
 - to address barriers to referral completion, as this will improve outcomes not only for severe malaria but also for other severe diseases; and
 - to ensure effective community sensitization to increase understanding of severe malaria, its causes, how dangerous it is for children, how to recognize danger signs and the need to promptly seek care if such signs are present.

Risk mitigation (contd)

- Malaria programmes and their partners should ensure that health providers adhere strictly to malaria treatment guidelines and make sure that caregivers of children with severe malaria are aware of the importance of completing treatment courses. Intense efforts should be made to ensure that:
 - artemisinin-based monotherapies (both rectal and parenteral) are used only for treating severe malaria cases as per WHO guidelines;
 - referral facilities treat severe malaria patients with parenteral artesunate and a full course of an effective ACT;
- Antimalarial resistance surveillance should be strengthened at the population level across Africa, and most urgently in East Africa, with:
 - prioritization of interventions to holistically address the drivers of resistance selection;
 - prompt response in line with the WHO Strategy to respond to antimalarial drug resistance in Africa when resistance is detected.

Next steps

- Publication of the WHO Implementation Manual for Effective Deployment of Rectal artesunate as pre-referral treatment of malaria.
- Support countries in the effective deployment of RAS, through strengthening of the quality of care across the entire continuum of care and services.

Thank you