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

2023 update

In 2021, preliminary results of observational studies from the Community Access to Rectal Artesunate for Malaria (CARAMAL) project were presented to the World Health Organization (WHO) Global Malaria Programme and the Malaria Policy Advisory Group. These results did not confirm the mortality impact observed in the controlled trial in 2009. Consequently, in January 2022, WHO released an information note on rectal artesunate (RAS), suggesting immediate risk mitigation measures.

To provide clarity on the evidence, in October 2022, WHO convened a technical consultation of independent experts to conduct a formal evidence review of the data from the CARAMAL project, as well as data from other studies evaluating the deployment of pre-referral RAS at programmatic level *(1)*. The outcomes of the review, including results of additional analyses undertaken by the WHO-appointed experts, form the basis of this 2023 update on the use of RAS as a pre-referral treatment for severe *Plasmodium falciparum* malaria.

Background

WHO recommends that:

> "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 (10 mg/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" *(2)*.

For successful treatment of suspected severe malaria in children, the administration of a single dose of RAS must be followed by immediate transfer to an appropriate facility for intensive nursing care and treatment with injectable artesunate, followed by a full three-day course of an artemisinin-based combination therapy (ACT) once the patient can tolerate oral medication.

World Health Organization

The adoption and deployment of RAS at country level has progressed at a slow pace. RAS only became available at a quality-assured standard in 2018, with the WHO prequalification of two 100 mg products – a key prerequisite for the large-scale procurement of the commodity using multilateral funds *(3)*. Between 2018 and 2021, nearly 7 million WHO-prequalified suppositories were procured by 36 countries, 30 of which were located in Africa. As of 2021, a total of 54 countries had adopted pre-referral treatment of malaria with artesunate, artemether or quinine.

From efficacy to effectiveness

The efficacy of pre-referral RAS was evaluated 15 years ago in a large individually randomized placebo-controlled trial involving children and adults in Bangladesh, Ghana and the United Republic of Tanzania *(4)*. In this study, in which participants were assured referral and a high quality of care, administration of RAS reduced mortality by about 25% in children under 6 years, but was associated with a doubling of mortality in older children and adults.

To address specific research questions and to develop operational guidance for the implementation and scale-up of RAS, the Unitaid-funded CARAMAL project was conducted between 2017 and 2021 as a large-scale observational study in three African countries (the Democratic Republic of the Congo, Nigeria and Uganda).

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 study design was powered to detect a reduction in the case fatality rate (CFR) among children receiving RAS using pooled data from the three participating countries. However, during the study, it became apparent that the health care systems and baseline CFRs for severe malaria differed substantially between countries. Therefore, each country was analysed separately, even though the study was not designed or powered for such analysis; this substantially reduced the power of the study to detect the effects of RAS. The primary analysis compared children who received RAS to those who did not. The untreated group included all severe malaria cases in the pre-RAS period, with potential temporal confounding given the evidence, at least in Nigeria, that the CFR was substantially lower in the pre-RAS period than in the post-RAS period, including among children untreated with RAS in the post-RAS period. The measured differences and temporal confounding between the RAS user and non-user groups (pre-and post-RAS periods) were not suitably accounted for in the analyses. Therefore, it is difficult to interpret the relationship between RAS use and change in CFR in the CARAMAL project.

The CARAMAL project, however, highlighted many challenges and deficiencies along the cascade of care, revealing health system weaknesses and inadequate quality of care. For example:

- Among those who received RAS, a large proportion did not receive the required full dose for their age.
- Overall referral completion was low. Referral completion was not associated with RAS use in the Democratic Republic of the Congo or in Uganda, but it was lower among RAS users (73%) than among non-users (95%) enrolled by Nigerian community health workers.
- Post-referral treatment was often incomplete; in particular, treatment with injectable artesunate was suboptimal and the required three-day ACT treatment was not consistently administered.

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. At the end of that study, there were fewer stockouts of RAS, better knowledge of the signs of severe malaria among the community health workers (CHWs) and better knowledge of how to manage severe malaria among health workers at health facilities.

Artemisinin resistance

In a substudy 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 (Kole and Oyam, but not Kwania districts) and in other districts (e.g. Lamwo and Agago districts) where RAS was not deployed. Uptake of RAS and treatment-seeking from community health workers appeared very low in Uganda (less than 1% in household surveys among children with symptoms of severe malaria). Similar increases in resistance markers were not seen in the CARAMAL study sites in the Democratic Republic of the Congo or Nigeria.

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. This mutation was shown to have emerged locally in East Africa and to be associated with increased tolerance to artemisinins in the ring-stage survival assay.

Risk mitigation

A. 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.

B. Malaria programmes and their partners in the public, nongovernmental organization and private sectors 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;
- appropriate supportive management treats concurrent infections that could be causing danger signs in a child with low-density parasitaemia; and
- initial rectal and/or injectable artemisinin-based monotherapy is always followed by a full oral course of an effective ACT.

C. 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; and
- prompt response in line with the WHO Strategy to respond to antimalarial drug resistance in Africa *(5)* when resistance is detected.

References

1. 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. Geneva: World Health Organization; 2023 (https://apps.who.int/iris/handle/10665/369637, accessed 21 June 2023).
2. WHO guidelines for malaria, 14 March 2023. Geneva: World Health Organization; 2023 (https://apps.who.int/iris/handle/10665/366432, accessed 8 May 2023). The guidelines are also available online at https://app.magicapp.org/#/guideline/7089. See https://app.magicapp.org/#/guideline/LwRMXj/section/noBQpL for the specific recommendation.
3. Medicines/finished pharmaceutical products [website]. In: WHO – Prequalification of Medical Products (IVDs, Medicines, Vaccines and Immunization Devices, Vector Control). Geneva: World Health Organization (https://extranet.who.int/pqweb/medicines/prequalified-lists/finished-pharmaceutical-products, accessed 8 May 2023).
4. Gomes MF, Faiz MA, Gyapong JO, Warsame M, Agbenyega T, Babiker A, et al. Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. Lancet. 2009;373(9663):557-66. doi: 10.1016/S0140-6736(08)61734-1.
5. Strategy to respond to antimalarial drug resistance in Africa. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/364531, accessed 8 May 2023).

The use of rectal artesunate as a pre-referral treatment for severe *Plasmodium falciparum* malaria, 2023 update

ISBN 978-92-4-007537-5 (electronic version)

ISBN 978-92-4-007538-2 (print version)

9789240075375