

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

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INFORMATION NOTE

The World Health Organization (WHO) Malaria Policy Advisory Group (MPAG) reviewed the evidence from a large-scale study in three African countries deploying rectal artesunate (RAS) under real-life conditions. As the highest advisory group to WHO on all malaria-related matters, MPAG issued a recommendation (1). This information note shares the findings of the study and possible implications for the use of RAS as pre-referral treatment for severe malaria and makes concrete recommendations for countries to consider.

BACKGROUND

WHO recommends that:

“where intramuscular injection of artesunate is not available, treat children < 6 years with a single rectal dose (10 mg/kg bw) of artesunate, and refer immediately to an appropriate facility for further care. Do not use rectal artesunate 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.

The adoption and deployment of RAS at country level has progressed at a slow pace. By 2017, 16 countries in Africa had included the use of RAS as pre-referral treatment in their national treatment guidelines, however, some of their recommendations were not fully aligned with WHO guidance (for example, recommending the use of RAS as a pre-referral intervention for patients over the age of 6). Moreover, RAS only became available at a quality-assured standard in 2018, with the WHO prequalification of two 100 mg products – a key factor for large-scale procurement of the commodity using multilateral funds (3). Between 2018 and 2020, about 3 million WHO-prequalified suppositories were procured by more than 20 countries.

EFFICACY AND 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 Community Access to Rectal Artesunate for Malaria (CARAMAL) project was conducted between 2017 and 2021 as a large-scale study in areas with functioning referral systems in three African countries (the Democratic Republic of the Congo, Nigeria and Uganda). RAS was administered to 88% of eligible patients in the Democratic Republic of the Congo, 52% in Nigeria, and 70% in Uganda. However, only a small proportion (< 10%) of the children enrolled in all three countries completed the full course of severe malaria treatment with injectable artesunate and an ACT. This study documented no positive effect on case fatality ratios (CFRs) following the introduction of pre-referral RAS under real-life conditions. The CFR evaluated at 28 days' follow-up was higher in all countries after the roll-out of RAS (6.7% vs. 6.6% in the Democratic Republic of the Congo, 16.1% vs. 4.2% in Nigeria, 0.7% vs. 0.3% in Uganda).

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

- Children received pre-referral RAS without meeting the criteria for severe malaria.
- Children who received RAS received an incorrect dose for their age.
- Referral completion was lower among children who received pre-referral RAS.
- Post-referral treatment was often incomplete; in particular, the required three-day ACT treatment was not consistently administered.

This inconsistent administration of the full three-day ACT raised additional concern over the extensive use of artemisinin monotherapy. This evidence comes in at a time when there is an increasing number of reports of *P. falciparum* parasites with an African genetic background and K13 mutations associated with delayed parasite clearance in a number of African settings. The lack of referral or failure to complete post-referral treatment results in the use of monotherapy for *P. falciparum* malaria, which could fuel the development and spread of artemisinin-resistant parasites. Indeed, in Uganda, a marked increase in the prevalence of K13 mutants was observed in a group of children who received RAS but had failed to complete the full course of ACT.

RISK MITIGATION

The reported findings raise significant concerns over the effectiveness of RAS in real-life settings, which are often associated with shortcomings in terms of referral and quality of care. Furthermore, the study documents the potential for harm and increased mortality if pre-referral RAS is not strictly implemented in line with existing WHO guidelines. Given the emergence and spread of antimalarial resistance in multiple countries of sub-Saharan Africa, incomplete adherence to the full ACT treatment could further contribute to artemisinin monotherapy.

- **Countries that have not yet introduced pre-referral RAS but are considering doing so should withhold implementation** and await further guidance from WHO on the criteria that need to be met to ensure the safe and efficacious use of RAS.
- **Countries that have already adopted and are deploying pre-referral RAS** should **urgently** review in detail the conditions under which it is currently being used. This includes all three steps along the cascade of care: (i) diagnosis and administration of RAS; (ii) immediate referral; and (iii) complete treatment with at least 24 hours of injectable artesunate and a three-day ACT. Countries that have already adopted pre-referral RAS are encouraged to **withhold further expansion** of its use until further guidance from WHO.

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.

REFERENCES

1. WHO Malaria Policy Advisory Group (MPAG) meeting, October 2021. Geneva: World Health Organization; 2021 (<https://apps.who.int/iris/handle/10665/348220>, accessed 19 January 2022).
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3. WHO Prequalified Lists of Finished Pharmaceutical Products [online resource]. Geneva: WHO (<https://extranet.who.int/pqweb/medicines/prequalified-lists/finished-pharmaceutical-products>, accessed 8 November 2021).
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