CONCEPT NOTE - Severe Malaria Stakeholder Meeting 2022

Background

Malaria remains one of the leading causes of illness and death in children under 5 years old. In 2020, an estimated 627,000 people died from malaria globally, 77% of whom were children under 5 years old. The heaviest malaria burden is in sub-Saharan African countries, which account for an estimated 95 percent of malaria cases and 96 percent of malaria deaths in 2020[1].

A malaria infection may result in a wide variety of symptoms, ranging from absent or mild symptoms such as a headache or a fever (i.e., uncomplicated malaria) to multi-organ failure followed by coma and ultimately death (i.e., severe malaria). Severe malaria is typically linked to delayed treatment of uncomplicated malaria, often due to late treatment seeking and/or poor-quality case management. Mortality due to severe malaria, particularly cerebral malaria, if not treated, approaches 100%. With prompt, effective severe malaria treatment and supportive care, this rate falls to 10–20%, again depending on available care[2].

Patients with severe malaria should first be treated with intravenous or intramuscular artesunate for at least 24 hours and until they can tolerate oral medication. At this time, the patient should complete treatment with 3 days of an ACT. If parenteral artesunate is not available, artemether should be used in preference to quinine for treatment of children and adults with severe malaria.

Many patients with severe malaria live in remote settings with poor access to formal health facilities. In such settings, a confluence of factors (i.e., distance and time required to travel to facilities, lack and/or cost of available transport, etc.,) contribute to a patient's inability to promptly seek care, leading to delays in receiving a full and effective course of treatment and an increase in the risk of mortality. In remote situations where injectable artesunate (Inj AS) is not readily available, **artesunate rectal capsules (ARC)** also known as **rectal artesunate (RAS)** can be an effective pre-referral intervention for young children under six years of age.[2] RAS rapidly (i.e., within 24 hours) clears 90 percent or more of the malaria parasites and, and its impact on mortality as pre-referral treatment of severe malaria was evaluated in a single large individual randomized placebo-controlled trial involving 17 826 children and adults in Bangladesh, Ghana and the United Republic of Tanzania, in which pre-referral rectal artesunate was compared with placebo, followed by quinine parenteral treatment at referral hospital levels. Rectal artesunate administered this way reduced mortality by about 25% in children < 6 years and was associated with higher mortality in adults[3]. Until today, 14 randomized controlled clinical trials were conducted documenting the safety, tolerability, efficacy and the pharmacological characteristics of RAS[4].

[1] World Malaria Report 2021 (https://www.who.int/publications/i/item/9789240040496)[2] WHO Guidelines for Malaria, 13 July 2021 https://www.who.int/publications/i/item/guidelines-for-malaria

[2] WHO Guidelines for Malaria, 13 July 2021 https://www.who.int/publications/i/item/guidelines-for-malaria

[3] Gomes, MF, et al. (2009) Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. Lancet 2009; 373:557-66 DOI: 10.1016/50140-6736(08)61734-1.

[4] de Carvalho LP, Kreidenweiss A, Held J. The preclinical discovery and development of rectal artesunate for the treatment of malaria in young children: a review of the evidence. Expert Opinion on Drug Discovery. 2021;16(1):13-22.

RAS administration must be followed by immediate transfer to an appropriate facility for intensive nursing care and treatment with injectable artesunate followed by a full 3-day ACT treatment, once the patient can tolerate oral medication[5].

Despite WHO recommendations since 2006, adoption and use of RAS and Inj As remained fairly stagnant over the first 5 to 10 years. Developments in recent years, however, are rapidly changing this landscape. Investments from Unitaid have led to two WHO- prequalified products in both product categories: a WHO prequalified Inj As product (30mg, 60 mg, 120 mg) produced by Guilin, available since 2011, is now complemented by the recent prequalification of an Ipca Inj As product (60 mg). For RAS, a CIPLA and a Strides 100 mg product received prequalification status in 2018. Some countries have already started using RAS and others are poised to scale use of RAS and Inj AS over the coming years, with large donors including PMI and the GFATM meeting country requests for increased procurement of both products.

Yet, significant challenges remain. RAS is a pre-referral intervention intended for use in children under six years of age at the peripheral level as part of a severe malaria treatment system that includes referral and appropriate management with Inj AS at a higher-level facility. RAS relies on strong iCCM/community services to provide access to prompt diagnosis and effective treatment of uncomplicated malaria care and referral of children with severe febrile illnesses. When introduced into functional iCCM platforms, RAS can work effectively as continuum of care requires efficient referral and appropriate and complete post-referral care. Many of the countries where the product may have a significant impact on malaria mortality remain unprepared to introduce RAS in an appropriate, safe way, due to weak or nonexistent iCCM platforms, severe and persistent barriers to referral barriers, inadequate management of severe malaria at hospital level at and/or inadequate post-referral care. A recent landscape assessment[6] found that even in countries where national guidelines align with those of the WHO, many countries did not have community-based health services to deliver RAS into a functional continuum of care.

Improved management of severe malaria requires comprehensive assessment and improvement of the whole pre-referral, referral and treatment pathway, from early recognition and access to care including the provision of RAS at peripheral level, to improved referral to and treatment practices at the referral facilities of care. Scaling RAS in communities unprepared to manage and refer severely ill children will not reduce malaria mortality and may expose severely ill children to incomplete treatment.

The CARAMAL project (Community Access to Rectal Artesunate for Malaria) was designed to generate evidence to support the development of operational guidance for the implementation and scale-up of RAS, since RAS has become commercially available at a WHO-prequalified standard, enabling large-scale procurement with international financing. The project relied on two components: RAS implementation in the context of established Integrated Community Case Management (iCCM) programmes; and a large operational research component.

Project findings demonstrated reduced referral completion, leading to incomplete treatment and missing of other infections and comorbidities. Post-referral treatment was often incomplete and, in

[5] Guidelines for treatment of malaria, WHO, 3rd Edition (2015)

[6] CHAI conducted a landscape assessment of rectal artesunate (ARC) procurement and use as part of Output 4 in 2018

particular, the required three-day ACT was not consistently administered, leaving patients with RAS/injectable artesunate as artemisinin monotherapy[7].

Proposal

Building on Inj AS and RAS stakeholder meetings in 2011[8] and 2016[9] respectively, and on the Severe Malaria Stakeholder Meeting held in 2019 in Abuja https://www.severemalaria.org/resources/severe-malaria-stakeholder-meeting-21-22-october-2019-abuja we propose **a second global stakeholder meeting on severe malaria case management** to bring together a wide range of stakeholders in early February 2022. The last stakeholder meeting held in October 2019 assembled countries that had commenced the process of rolling out RAS within their systems of severe malaria care. The objective of that meeting was to **share experiences** from ongoing efforts to improve the continuum of severe malaria care from community (i.e., RAS) to referral facility (i.e., Inj AS). This second stakeholder meeting, to be held in early February 2022, will serve as a platform to (1) **share results and lessons learnt** from operational research projects such as CARAMAL and other pilots, studies and implementation experiences since 2019 and (2) **disseminate new WHO guidance** on the use of RAS . The key objective of this meeting is to inform the malaria community, specifically NMCPs, on the latest information/evidence on the use of RAS and to discuss implications these may have on operational guidance and scale up plans of RAS.

Proposed Format for Stakeholder Meeting II: 8-9 February, 2022 (virtual format)

The 2022 stakeholder meeting will be a virtual meeting, composed of plenary sessions, panels of experts, and action-oriented country-by-country brainstorming.

Key topics/themes of the meeting may include:

Day 1: Latest information/evidence on RAS and Injectable AS + ACT use

- Progress update toward adoption of RAS globally
- RAS implementation experiences from CARAMAL and beyond
- Latest WHO operational guidance on RAS use deriving from CARAMAL findings
- Artemisinin resistance update in Africa
- Update on RAS formulations and temperature stability under field conditions

Day 2: Implications for RAS and Injectable AS + ACT use as part of the continuum of care

[7] Malaria Policy and Advisory Group Meeting Report October 2021. https://www.who.int/news-room/events/detail/2021/10/04/default-calendar/20th-meeting-of-the-malaria-policy-advisory-group.
[8] https://www.severemalaria.org/sites/mmv-smo/files/content/attachments/2017-01-27/Injectable_Artesunate_Stakeholders_Meeting_Report_3.pdf
[9] https://www.mmv.org/newsroom/publications/rectal-artesunate-stakeholders-meeting-report

- Implementation implications in CARAMAL countries and beyond, to be in line with new WHO recommendation
- Programmatic and funding implications

Attendees:

- National Malaria Control Programs *(primary target audience)*
- Ministry unit(s) involved in implementation of community case management or iCCM
- Research Institutions investing in RAS operational research
- Research Institutions with expertise in assessment of observational studies
- Donors in malaria space
- Technical agencies supporting NMCP in Implementing iCCM and RAS as part of continuum of care

Organizing partners: MMV and CHAI under the auspices of the RBM Case Management Working Group, in collaboration with WHO, PMI, and GFATM, with inputs from CARAMAL team

Funding: Unitaid

Dates (8-9 February 2021): two 3 hour sessions (6 hours meeting in total)

Location: Via Zoom or MS Teams

Expected outputs from this meeting:

- Meeting report which will be disseminated via the RBM Case Management Working Group and the Severe Malaria Observatory
- Identification of countries where additional support may be required