

# Rectal Artesunate Stakeholders' Meeting Report

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## KEY FACTS<sup>1</sup>

- There were an estimated 214 million cases of malaria globally in 2015.
- The incidence of malaria, which takes into account population growth, is estimated to have decreased by 37% between 2000 and 2015. In total, 57 of 106 countries that had ongoing transmission in 2000 have reduced malaria incidence by >75%.
- The number of malaria deaths globally in children aged under 5 years is estimated at 306,000 in 2015, down from 723,000 in 2000.
- In the absence of treatment, mortality from severe malaria approaches 100%. With prompt, effective antimalarial treatment and supportive care, mortality is reduced to 10-20%.<sup>2</sup>

## BACKGROUND

Despite impressive reductions in malaria morbidity and mortality since 2000, more than 300,000 children under five years of age died from malaria in 2015; the majority of these deaths occurred in sub-Saharan Africa. Reducing malaria deaths to near zero is a key public health priority in Africa. Effective management of patients presenting with signs of severe malaria at the periphery of health services is vital in the fight to end malaria deaths. The role of community health workers (CHWs) in recognising malaria danger signs and providing early effective treatment as part of integrated Community Case Management (iCCM) is critical as prompt and effective treatment of severe malaria cases can significantly reduce malaria mortality.

In situations of likely severe malaria where parenteral medication is not available, the World Health Organization (WHO) recommends to pre-treat children < 6 years with a single rectal dose (10mg/kg) of artesunate (RAS) and refer immediately to an appropriate facility for further care and definitive malaria treatment. RAS is an effective pre-referral intervention as it rapidly clears 90% or more of malaria parasites<sup>3</sup> and reduces the risk of death or permanent disability in young children, as long as this initial treatment is followed by appropriate parenteral antimalarial treatment in a hospital and a full course of artemisinin-based combination therapy (ACTs).<sup>4</sup> If, however, referral is impossible, rectal treatment should be continued according to the guidelines until the patient can tolerate oral medication, at which point a full course of the recommended ACT for uncomplicated malaria can be administered<sup>5</sup>.

Sixteen countries currently include RAS and injectable artesunate (Inj AS) in their treatment guidelines. No globally commercially available WHO-GMP approved formulation of RAS exists as yet, but two RAS products (developed by Strides and Cipla) have recently been submitted for WHO prequalification, opening the way for wide-scale implementation after approvals have been granted.

## STAKEHOLDER MEETING FRAMEWORK

On 19 February 2016, stakeholders from 13 organizations<sup>6</sup> spanning the field of malaria prevention and control, seven malaria-endemic countries in Africa (Democratic Republic of Congo, Burkina Faso, Malawi, Central African Republic, Kenya, Uganda and Zambia) and the WHO came together to discuss experiences, challenges and overcoming obstacles relating to the implementation of RAS as a pre-referral intervention for the management of severe malaria in children. The meeting was co-convened in Nairobi, Kenya by Medicines for Malaria Venture (MMV), the US President's Malaria Initiative (PMI), UNICEF and Médecins Sans Frontières (MSF).

This report of the RAS Stakeholder Meeting summarises the key issues relating to the adoption and implementation of RAS in malaria-affected regions and outlines recommended actions to speed up access to this life saving medicine.

### References

1. World Health Organization Global Malaria Programme (2015). World Malaria Report 2015.
2. World Health Organization (2015). Guidelines for the Treatment of Malaria. Third Edition.
3. Gomes, M, Ribeiro, I, Warsame, M, Petzold, M. (2008) Rectal artemisinins for malaria: a review of efficacy and safety from individual patient data in clinical studies. *BMC Infectious Diseases* **8**:39 doi:10.1186/1471-2334-8-39.
4. World Health Organization (2015). Guidelines for the Treatment of Malaria. Third Edition.
5. World Health Organization (2015). Guidelines for the Treatment of Malaria. Third Edition.
6. CHAI, CDC, IFRC, Malaria Consortium, MMV, MSF, PFSCM i+ solutions, PSI, Save the Children, UNICEF, UNITAID, USAID, US-PMI.

## IMPLEMENTATION OF PRE-REFERRAL MANAGEMENT USING RAS

Management of severe febrile illness at the community level includes two components: treatment of the patient by the CHW using RAS as pre-referral intervention and referral to a health facility where full treatment of severe malaria, including administration of injectable antimalarials followed by a full treatment of an ACT, may occur. Effective and safe implementation of RAS at the periphery of the health system is dependent on several factors, including:

### Community Level:

- Well-trained CHWs able to identify malaria danger signs (severe febrile illness) and administer RAS.
- Availability of RAS for pre-referral management of severe febrile illness at community level.
- Awareness among caregivers and the wider community of danger signs and of the importance of early treatment seeking.

### Health Facility Level:

- Functional referral systems for referring patients to the next health care level, where the diagnosis of malaria can be confirmed and intravenous artesunate (or where not feasible, the next best treatment as recommended by the WHO treatment guidelines) can be administered by healthcare workers trained in the management of severe malaria.
- Availability of medicines for the treatment of severe malaria.
- Effective procurement and supply management (PSM) systems.
- Effective and comprehensive monitoring, evaluation and supervision.

### The recommended regimen for RAS is 10mg/kg in a single dose.

- A single rectal capsule of 100 mg should be given to paediatric patients with a body weight of 5 kg to 14 kg or age 6 months to (and including) 36 months.
- Two rectal capsules of 100 mg each should be given to paediatric patients with a body weight of greater than 14 kg to 20 kg or aged greater than 36 months up to 72 months.

## COUNTRY EXPERIENCES AND KEY ISSUES

Field experience from two countries, DRC and Malawi, currently piloting RAS indicate that it saves lives and is well accepted by communities, CHWs and facility-based health workers.

Some countries expressed concern that the speed and effectiveness of RAS in resolving symptoms of severe malaria might potentially affect compliance with referral and/or create demand for use of RAS in treatment of non-severe cases.

DRC and Malawi, who presented case studies of RAS rollout, specifically indicated that caregiver compliance with referral was better than expected.

### Recommendations ▼

#### Optimize RAS pre-referral system within countries

- Countries need to improve referral systems and facilitate effective referral of severely ill patients

#### Ensure optimal conditions for RAS implementation

- Track expiry of RAS commodities to minimize waste and ensure efficiency and cost-effectiveness.
- Incorporate monitoring of RAS implementation into existing national community health Monitoring and Evaluation systems, as part of the wider Health Management Information System.
- Facilitate use of e-health technologies, including District Health Information System 2 (DHIS 2) mobile and other smartphone applications.
- A rapid diagnostic test for malaria is NOT a prerequisite for administration of RAS according to the WHO guidelines<sup>7</sup>. Any delays caused by waiting for a definitive diagnosis could prove fatal and must be avoided.

#### Build community awareness of RAS to promote acceptance

- CHWs can help raise community awareness about RAS and also should inform and educate caregivers on the importance of compliance with referral.

## TRAINING AND SUPPORT

The need for effective training of both community and facility level healthcare personnel is critical for successful implementation. The addition of RAS as a new intervention to the iCCM package should not present any major challenges in terms of community acceptance, health worker training and skills upgrading.

MMV, with support from other stakeholders, has developed RAS training materials<sup>8</sup>; these materials can be adapted for incorporation into local materials, ensuring that all key components are included, e.g. danger signs and importance of referral.

There are challenges in training CHWs on the practical aspects of administering RAS.

### Recommendations ▼

#### Define targets and content of RAS training

- Train or update the skills of CHWs and health facility staff in diagnosing and treating malaria, as well as on other components of iCCM, as part of RAS training.
- Train CHWs, supervisors and health facility staff on RAS.
- Include: determining dosages by age and weight, insertion of the rectal capsules, counselling of caregivers, the referral process and community mobilization and orientation in training curriculum.
- If applicable, engage private sector facilities in training activities to avoid potential conflict with public health systems.
- Define and adapt RAS training packages at country level, including the provision of practical training and minimum requirements for certification/qualification of CHWs.
- Adapt training materials for the different levels of the health system, reflecting differences in capacities and authorized scope of practice.

#### Supportive supervision

- Conduct periodic assessment of CHW skills and provide refresher training to ensure that the skills acquired in administering RAS are maintained even though numbers of patients presenting with severe symptoms are likely to be very low.
- Strengthen links between CHWs and facilities, such as innovative approaches to supportive supervision and mentoring.
- Improve supervision, mentoring and refresher training to avoid unnecessary and costly training.
- Adopt mobile-health, or other smartphone based technologies and audio-visual media to reduce recurrent costs of further CHW training.
- Use m-health and other technologies to monitor CHW performance and guide supportive supervision and mentoring.

#### References

7. World Health Organization (2015). Guidelines for the Treatment of Malaria. Third Edition.
8. <http://www.mmv.org/access/rectal-artesunate-tool-kit>

## OVERCOMING OBSTACLES

| Obstacle ▼  | Recommended Solution ▼  |
|---|---|
| <b>Motivation of CHWs</b>   | <ul style="list-style-type: none"> <li>• Shift to a system of government-funded financial remuneration of CHWs.</li> <li>• Implement effective, regular supportive supervision and feedback.</li> </ul>   |
| <b>Lack of effective referral systems</b>                             | <ul style="list-style-type: none"> <li>• Identify options and mechanisms to support compliance with referral, e.g., bicycle ambulances, use of 'referral slips', etc.</li> </ul>  |
| <b>Misuse of RAS</b>  | <ul style="list-style-type: none"> <li>• Optimise packaging.</li> <li>• Simplify dosages – Products undergoing prequalification will be available as 100 mg capsules only.</li> <li>• Develop CHW targeted algorithms for administration – possibly including a checklist.</li> </ul> |
| <b>Quantification of need and procurement and supplies management</b> | <ul style="list-style-type: none"> <li>• Strengthen PSM planning and strengthen national and sub-national warehousing and distribution systems.</li> <li>• Implement 'pull' system for resupplying CHWs.</li> </ul>   |
| <b>Commodity storage</b>  | <ul style="list-style-type: none"> <li>• Utilize existing cool-storage options or provide improved medicine boxes for CHWs in areas where high temperatures are common.</li> <li>• Investigate alternative low-tech storage solutions.</li> </ul>                                     |
| <b>Parasite resistance</b>  | <ul style="list-style-type: none"> <li>• Close supervision and monitoring of RAS deployment should significantly reduce the risk of increased artemisinin resistance from misuse by CHWs.</li> </ul>  |

## SUPPORTIVE INTERVENTIONS

### ***Behaviour Change Communication and Operational Research***

Behaviour Change Communication (BCC) is a vital component of RAS implementation and scale-up. Caregivers and parents must be able to recognise malaria danger signs and understand the importance of prompt treatment-seeking and of compliance with referral in order to achieve a full cure. The community needs to be sensitised to RAS as a new pre-referral option. CHWs and facility-based staff need to be sensitised and trained on correct RAS use, including the need for referral to the next level.

### **Recommendations - BCC ▼**

|   |  |
|---|--|
| <b>Understand existing community knowledge and behaviours</b> | <ul style="list-style-type: none"> <li>• Undertake a baseline study of knowledge and practices and fears around severe febrile illnesses and sensitise communities about the intervention.</li> <li>• Identify the places or communities where direct access to a health centre is problematic and where patients with severe danger signs should first contact a CHW.</li> </ul>  |
| <b>Identify most appropriate communication channels</b>       | <ul style="list-style-type: none"> <li>• Use CHWs, local traditional community leaders, political structures, religious institutions, community radio and other media to spread messages. The testimony of peers regarding the effectiveness of RAS will be a key factor in promoting acceptance and compliance.</li> <li>• Avoid the risk of 'message fatigue' through innovative and adaptable approaches to community sensitization and BCC.</li> </ul> |
| <b>Emphasize behaviour change and community awareness</b>     | <ul style="list-style-type: none"> <li>• Ensure that community members can recognize danger signs and take timely and appropriate action to obtain treatment and comply with referral.</li> </ul>  |

## Recommendations - Operational Research ▼

Prior to developing an operational research agenda for RAS, there is a need to document and understand the current status of RAS implementation within target countries.

### Operational Research Topics

#### Optimize RAS pre-referral systems within countries

- Need to determine what referral systems best lend themselves to scalability and sustainability.

#### Ensure optimal conditions for RAS implementation

- Develop and test quantification models and tools that reflect the changes in epidemiology of severe malaria as prevention and control interventions reduce case incidence.
- Identify alternative case management options where RAS is not possible (e.g. severe diarrhoea).
- Develop and test innovative approaches to improve quality of care at CHW and first level health facility levels.
- Develop innovative approaches to accessing and creating demand for health services among communities and individuals not currently using the formal health care system.

#### Measures and Indicators

- Determine duration from when the child is referred from the community to the healthcare facility and initiation of injectable AS.
- Determine percentage of children who complete a full course of treatment for the episode of severe malaria.
- Identify factors facilitating and impeding adherence to the referral.
- Adapt HMIS and DHIS platforms to record and report RAS data, including referral.

## SUMMARY

In the few countries where RAS introduction has been piloted, there is acceptance of RAS by caregivers and communities, CHWs and health facility staff.

Given the importance of reinforcing referral after RAS administration in order to reduce child mortality, there is a pressing need for national community health programmes to explore potential options to improve referral systems and facilitate effective referral of severely ill patients.

Concerns exist about the risk of accelerating the development of parasite resistance through inappropriate overuse of RAS (e.g., for treatment of uncomplicated malaria) or through failing to follow pre-referral use of RAS with injectable artesunate treatment until the patient is able to take a full course of oral ACTs. However, reinforcing supervision and monitoring of RAS use should ensure that only the sickest of children with severe malaria will be treated with RAS and that these patients receive appropriate follow-on treatment.

Some challenges remain, including difficulties in the quantification of likely RAS demand, given that the number of severe cases seen at peripheral levels of the health service will be low and unpredictable. Maximising the efficiency of national PSM systems to ensure no stock-outs and ensure 'last mile' delivery of commodities to CHWs is required.

iCCM is being progressively embraced as a branch of primary health care and there is an excellent chance of RAS succeeding as a vital component of severe malaria management at community level. However, to guarantee its success, there is a need to focus on all core arms of the health service, not solely on the periphery.



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