Severe Malaria Global Stakeholder Meeting

21-22 October 2019,
Abuja, Nigeria

Defeating Malaria Together

MMV
Medicines for Malaria Venture

Abbreviations

ARC	Artesunate Rectal Capsules (or RAS = rectal artesunate)
CARAMAL	Community Access to Rectal Artesunate for Malaria
CHAI	Clinton Health Access Initiative
CHW	Community Health Worker
CRS	Catholic Relief Service
GFATM	The Global Fund to Fight AIDS TB and Malaria
iCCM	Integrated Community Case Management
Inj AS	Intramuscular Artesunate Injection
KSPH	Kinshasa School of Public Health
MMV	Medicines for Malaria Venture
MSF	Médecins Sans Frontières
MSH	Management Sciences for Health
NURTW	National Union of Road Transport Workers
RBM	Roll Back Malaria
PMI	President's Malaria Initiative
Swiss TPH	Swiss Tropical and Public Health Institute
WHO	World Health Organisation

Executive Summary

Background

Medicines for Malaria Venture (MMV) and the Clinton Health Access Initiative (CHAI) convened a Severe Malaria Global Stakeholder Meeting, under the auspices of the RBM Case Management Working Group and in collaboration with UNICEF, Swiss Tropical and Public Health Institute (Swiss TPH) and Médecins Sans Frontières (MSF). The meeting was hosted by the Nigerian Ministry of Health in Abuja, Nigeria and held on the 21st and 22nd of October, 2019.

This was the first meeting convened on severe malaria case management, building on stakeholder meetings focused on Injectable artesunate (Inj AS) and artesunate rectal capsules (ARC) in 2011 and 2016, respectively. The meeting assembled countries that have commenced the process of rolling out rectal artesunate within their systems of severe malaria care.

The meeting brought together delegations representing 19 countries: Angola, Benin, Burkina Faso, CAR, Congo, DRC, Ethiopia, Ghana, Liberia, Madagascar, Malawi, Mali, Mozambique, Niger, Nigeria, Sierra Leone, Uganda, Zambia and Zimbabwe, and 15 partner organizations, including RBM, Unitaid, PMI USAID, Global Fund, UNICEF, MSH, Swiss TPH, Akena, KSPH, CRS, Makarere University, MSF, PSI, WHO and the Malaria Consortium.

Aims and objectives

The key objective of the meeting was to share experiences from existing efforts to improve the continuum of severe malaria care from community to referral facility levels, incorporating rectal and injectable artesunate. The ultimate goal of the meeting was to promote better patient care and reduce mortality from severe malaria.

The meeting sessions

DAY 1

The meeting was introduced with a short review of updated WHO recommendations on pre-referral interventions and treatment of severe malaria, an overview of the currently available WHO prequalified severe malaria products (Artesunate Rectal Capsules (ARC) and Injectable Artesunate (Inj AS)), highlighting that an appropriate ACT is required to complete severe malaria treatment, and an update on ARC and Inj AS procurement and guideline alignment in endemic countries.

The meeting day was structured according to the following themes, each highlighting a different aspect of ARC and Inj AS implementation and deployment:

Theme 1: Coordination in funding and implementation

During this session, experiences and perspectives from countries and donors were shared, and opportunities and ways forward to ensure stronger national leadership, improve coordination and address health system related challenges were discussed.

Theme 2: Service delivery pre- and post-referral

Country presentations reflected on real-life experiences in the roll out of ARC and Inj AS along a continuum of care. Challenges included complications in completion of referral, especially in remote settings, stock management and correct use of artesunate products. Lessons learnt in addressing these problems were shared, including formal involvement of the private sector.

Theme 3: Referral

Presentations and discussions focussed on the need for communities' active participation in referral systems, the importance of community-supported emergency transport systems and the crucial and potentially life-saving role of community health workers as a first point of care. It was discussed that countries should move towards compensating community health workers (CHWs) as accountable workers within the health system, and that up from the first level facility, transport for referral should ideally be part of the formal health care services.

Theme 4: Logistics and supply chain management

A compilation of currently available data on the stability of ARC were presented by MMV as well as storage solutions for ARC at community level in Uganda and DRC. The presented preliminary stability data suggest ARC is stable for at least 18 months at temperatures up to 30°C, and for short periods (up to 3 months) at 40°C. However, more robust data are required to revise current WHO recommendations and approved SmPCs which must continue to apply (i.e. "Do not store above 25°C. Avoid excursions above 30°C").

DAY 2

On day 2, 8 countries (Angola, Madagascar, Malawi, Mozambique, Nigeria, Uganda, Zambia and Zimbabwe) participated in workshops and reported on the key themes from day 1: 1) Coordination, 2) Service delivery pre- and post-referral, 3) Referral, 4) Supply chain, with an additional topic included on Surveillance.

Meeting Conclusion

The meeting was concluded with an invitation to countries to develop concrete action plans for the next 12 months for the successful implementation of ARC and Inj AS, along the lines of the meeting themes.

Introduction

Malaria remains one of the leading causes of illness and death in children under 5 years old. In 2018, an estimated 405,000 people died from malaria globally, 61% of whom were children under 5 years old. The heaviest malaria burden is in sub-Saharan African countries, which accounted for an estimated 92% of malaria cases and 93% of malaria deaths in 2018.[1] Severe malaria is linked to delayed treatment of uncomplicated malaria, often due to late treatment seeking or poor quality case management. Mortality from untreated severe malaria (particularly cerebral malaria) approaches 100%. With prompt, effective severe malaria treatment and supportive care, this rate falls to 10–20%.[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 IM should be used in preference to quinine for treatment of children and adults with severe malaria.

Many patients with severe malaria, however, live in remote settings with poor access to health facilities. Where Inj AS is not available, ARC is an effective pre-referral intervention recommended for young children under 6 years of age. ARC rapidly (i.e., within 24 hours) clears 90% or more of the malaria parasites in children younger than 6 years of age and can reduce the risk of death or permanent disability by up to 50%.[3] Administration of ARC must be followed by immediate referral of the patient to a higher-level facility where the complete treatment for severe malaria can be provided, which includes Inj AS and an appropriate ACT.

Despite WHO recommendations since 2006, adoption and use of ARC and Inj AS remained fairly stagnant over the first 5 to 10 years partly due to limited availability of products and slow uptake by countries. Developments in recent years, however, are rapidly changing this landscape as quality-assessed injectable and rectal products have become available. 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 ARC, both CIPLA and Strides 100 mg products received prequalification status in 2018.

> “In 2018, an estimated 405,000 people died from malaria globally, 61% of whom were children under 5 years old.”

Inj AS is now registered in 33 countries, and ARC in 16 countries globally. Many countries have already started using ARC and others are poised to scale up the use of ARC and Inj AS over the coming years, with large donors including PMI and GFATM pledging their support through increased funding for the procurement of both WHO prequalified injectable and rectal products.

1. World Malaria Report 2019. WHO.
2. WHO Guidelines for the Treatment of Malaria, 3rd edition, 2015. WHO.
3. Gomes MF *et al.* Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. Lancet. 2009, Vol. 373, pp. 577-66.

Stakeholder meeting rationale and purpose

This meeting aimed to serve as a timely platform for countries to share experiences of severe malaria case management, including sharing of initial experiences from the multi-country Community Access to Rectal Artesunate for Malaria (CARAMAL) project.[4] It provided attending countries with an opportunity to receive information for implementation plan development, taking into account the next GFATM funding cycle. The agenda for the meeting was structured around responses to a questionnaire (see annex 2) shared with invited countries prior to the meeting in order to help prioritize which topics or themes should be included in the meeting agenda.

This report will provide an overview of the contents and discussions of the meeting, outline trends across countries and specify any next steps and conclusions.

DAY 1

Day 1 sessions were divided into four themes: (1) Coordination in funding and implementation; (2) Service delivery pre- and post-referral; (3) Referral; and (4) Rectal artesunate supply chain and stability guidance. Preliminary experiences from the CARAMAL project and findings from MMV's rapid assessments[5] across DRC, Liberia and Uganda formed the basis for discussion and reflection in the sessions.
> A complete agenda can be found in annex 1.

Theme 1: Coordination in funding and implementation

Strengthening of severe malaria case management requires coordination with multiple actors, funding streams, supply lines and implementing agencies. It also requires harmonization of NMCP, child and community health programs, national supply chain management and pharmacy departments' policies and guidelines. In pre-meeting questionnaire responses, many countries identified coordination in funding and implementation as a priority area of discussion.

The objective of this session was to share experiences and perspectives on coordination in funding and implementation, including challenges and opportunities.

Three countries (Nigeria, Uganda and DRC) shared their experiences, successes and challenges in the area of malaria coordination. Each country provided background information on their severe malaria systems and one example of an effort to combat challenges of coordination. Additionally, a presentation from PMI gave an overview of funding and coordination from the donor perspective.

Challenges and good practices

Coordination between donors and national programs can be challenging, and there is a need for a better alignment of priorities, financing cycles and commodity orders. Planning is the government's responsibility, but implementation is often led by partners, resulting in a lack of coordination and information flow. This can result in interventions based on available funding rather than in-country needs. For example, in Nigeria, funding decisions are often driven by donor policies, with 13 of 36 states still lacking any donor support.

National and state level advocacy to ensure that resources are aligned with needs ('giving Ministries of Health a strong voice') is crucial. In Uganda, there have been severe delays in accessing donor funding and poor alignment of donor and government's financial cycles has affected planning. Inflexible donor policies did not allow for reprogramming of funds.

Procurement of commodities for malaria remains donor-driven and is done according to donor's funding cycles, which can impact stock levels, supply chain plans, and commodity distribution systems. Most countries report a lack of funds for procurement of the full array of commodities (in particular non-malarial commodities) needed for the management of severe cases. This gap affects quality of care at all levels of the health system at all levels, from iCCM to primary, secondary and tertiary facilities. Support for severe malaria management should, in these countries, be expanded beyond ARC and Inj AS to capture the entire supply package of consumables required. To lessen donor dependency, in-country advocacy

4. Community access to rectal artesunate for malaria (CARAMAL) is a 3-year observational research study in DRC, Nigeria and Uganda, funded by Unitaid, that introduces ARC in communities through iCCM. CARAMAL aims to contribute to reducing malaria mortality in children by improving the community management of suspected severe malaria and advance the development of operational guidance for the scale-up of ARC. The evidence generated in the context of the CARAMAL project will be reviewed by WHO in 2021.
5. Reports are available on www.severemalaria.org

is needed to increase domestic funding for quality assured malarial and non-malarial commodities procurement. Irregular donor-driven drug supplies could, for example, be transitioned to a drug revolving fund model or other mechanisms to increase sustainability in the health system and reliable access to care. Proper procurement planning of severe malaria commodities is crucial, as only few supplies are WHO prequalified and lead times may be long.

Decision-making by donors lacks attunement to the reality on the ground. Quality data collection is often project-based, and does not take continuity and alignment with national systems into consideration. When quality data exist, these are often not used for decision-making. Regular review meetings with donors are recommended so that there is early engagement in case of trends, problems and anticipated changes. In Nigeria, working groups at national level (a Working Group for Severe Malaria which provides strategic advice and a Malaria Technical Working Group, coordinating all stakeholders) helped to focus attention on problems and ensure there are information feedback loops to implementers. To ensure working groups accurately represent the realities on the ground, a strong engagement with health workers is needed and a culture of data use should be nourished.

There is a need for improved coordination between major malaria donors, the main donors being GFATM and PMI-USAID. This has been recognized, and recent efforts by PMI have focused on harmonizing activities and funding categories with GFATM (including financial and supply chain data). In DRC, coordination with partners in the target areas (eg WHO, GFATM/SANRU) has been poor, and to respond to this critical gap the partners organized and executed a successful joint field mission which enabled information sharing and improved planning.

Theme 2: Service delivery pre- and post-referral

The continuum of care for malaria from identification of severe illness signs to care-seeking and then provision of care is not linear. One child may be taken to see numerous providers across public and private, formal and informal sectors. This child may or may not receive the complete care s/he requires. Improving quality of severe malaria care requires engagement of numerous stakeholders (including caregivers, CHWs, drug shops, and referral facility providers), and ongoing competency retention and quality improvement measurement at both pre- and post-referral levels of care. Based on pre-meeting questionnaire (see annex 2) responses, a session on service delivery from community to referral facility levels was included in the meeting.

Session objectives were to provide country specific experiences on quality of care at pre- and post-referral levels, including challenges and opportunities, and allow countries to assess how these experiences may be applicable to their own situation.

> “There is a need for improved coordination between major malaria donors”

Challenges and good practices

Regular stock outs of artesunate products, other iCCM commodities and equipment/ supplies needed to manage severe malaria at referral level is a highly challenging issue for weak health systems. Poor reporting at facility level and incomplete data flow to higher levels, often due to poor digital access, results in inaccurate quantification and suboptimal distribution of medicines. A number of countries are consistently either overstocked or under-stocked with AS products. Complicating factors are a lack of historical consumption data for ARC and suspected misuse of Inj AS for uncomplicated malaria. Challenges also exist in transportation of medicines to remote areas.

In DRC, Uganda and Nigeria, preliminary results from the CARAMAL project found inadequate severe malaria commodities in secondary and tertiary facilities for the management of severe malaria. In a survey of CHWs in Uganda, high levels of ARC (45%) and RDT (49%) stock out were observed in the previous 3 months (CARAMAL). In Nigeria, RDT stock-outs had occurred in 54% of communities and 17% of primary facilities in the last 12 months, while Inj AS was available in only 13% of primary facilities (CARAMAL).

In DRC, frequent stock-outs of Inj AS, ACT and RDTs occurred; MMVs rapid assessment of found that ARC had never been available in 40%, and was stocked out in 33% of health facilities. It also found that Inj AS had never been available in 60%, and was stocked out in 20% of health facilities.[6] Ensuring the continuous availability of medicines and other necessary commodities is crucial to achieve a continuum of care for severe malaria. Lessons learnt include the utilisation of routine data for stock management and distribution, and the redistribution of medicines and diagnostics between levels of facilities and from facility to community level as needed. Support for severe malaria management should preferably be combined with investments in strengthened reporting and supply management systems.

Poor adherence to guidelines, insufficient training in malaria case management and a lack of availability of treatment guidelines in facilities is common. This is complicated by a high turnover of human resources (HR) and a lack of retention of trained HR. Findings from MMV's rapid assessment found that updated malaria case management guidelines were available in only 27% of surveyed health facilities in DRC,[6] while in Liberia, 56% of surveyed health facilities had a case management training manual.[7] In Uganda, severe malaria was managed with varying levels of quality in secondary and tertiary facilities and depended on the level of training and the availability of equipment and supplies.[8] Diagnostic capacity at referral level in Uganda is underused: glycaemia and haemoglobin were most of the times not measured in surveyed facilities, despite equipment being in place (CARAMAL).

In-service training, mentoring and supervision in health facilities to improve adherence to treatment guidelines is essential for improving quality of care. Experience shows that gaps created by high staff turnover can be addressed by creating national repositories of health workers trained in severe malaria management.

Many severe malaria cases are treated at primary level. Case misclassification and poor referral practices are common. In DRC, severe malaria cases managed at primary level are known to be treated with quinine or other injectable drugs purchased by the patient. MMV's rapid assessment found that 75% of severe malaria patients were treated at the primary level instead of being referred to a higher level.[6] Referral rates in DRC may be lower than in other settings due to a number of factors including difficulties in referral completion (poor roads and limited transportation) and health facility reliance on consultation fees (primary health facilities can earn as much as 30 USD/case through sales of quinine and blood transfusion).

Morbidity and mortality in children after treatment for severe malaria is of concern. Under CARAMAL, enrolled children are assessed at day 28 after treatment. In Nigeria, preliminary results show 5% had died, 5% were still sick and around 80% were anaemic (<11 g/dl). Systematic follow-up of children post discharge, preferably at day 14 and 28, may be needed to develop approaches for reducing post-treatment morbidity and mortality.

There is continued wide-spread use of quinine; contrary to WHO guidelines which recommend Inj AS as the first choice (or injectable artemether as alternative), quinine is still in use in many countries and included as an alternative treatment in national treatment guidelines for severe malaria. In DRC, MMV's rapid assessment found that 69% of severe malaria patients treated at primary level received quinine. This quinine treatment was often under-dosed and not followed by ACT. Quinine injection was available in 80% of primary health facilities.[6] Where Inj AS stock out is common, completion of treatment for children who received ARC is often provided with quinine. Where there is local manufacturing of quinine, efforts to offer alternatives such as manufacturing and export of tonic water may help ease the process of phasing out the drug.

The following examples of incorrect use of AS products were reported by several countries:

- ARC underuse at community level due to unfamiliarity with the product
- Unexpected ARC use: in some health facilities there is no nurse employed at night and in this case, ARC is given instead of Inj AS
- Continuation / completion of severe malaria treatment with only ARC, rather than with the complete required treatment package which includes Inj AS and ACT
- No provision of ACT after administration of Inj AS
- Incorrect use of Inj AS for uncomplicated malaria

6. MMV, KSPH. Évaluation de la prise en charge des cas de paludisme grave en RDC: rapport préliminaire de l'étude.
7. https://www.severemalaria.org/resources/a-rapid-assessment-of-severe-malaria-management-in-liberia
8. https://www.severemalaria.org/in-the-field/projects/severe-malaria-assessment-uganda

The role of the private sector in the management of severe malaria is likely to be considerable. There is a lack of coordination between public and private health sectors and a lack of regulation, reporting and adherence to guidelines within the private sector. Inj AS sold in the private sector are mostly very expensive as compared to the public sector.

Pilot studies by CHAI and others demonstrated that investments in the private sector at the community level can improve malaria case management (at least for uncomplicated malaria); after training, supervision, linkage of drug shops to affordable high quality commodities and market shaping, the availability of iCCM commodities increased, prices of RDTs and ACT decreased and private provider knowledge improved. CHAI also supported the Ministry of Health in Uganda to introduce mTrac mobile weekly reporting to private health care providers and demonstrated that the private sector is able to consistently report quality data on febrile diseases.

Proposed good practices are to engage the private sector and involve regulatory bodies to enforce adherence to the guidelines. Providing training and mentorship in severe malaria case management to the private sector should improve provider knowledge, and could possibly have a positive impact on quality, availability and prices. Rolling out a convenient reporting system in the private sector could help generate consistent quality data.

Theme 3: Referral

The severe malaria continuum requires prompt and accessible transfer of severely ill patients from community to a higher level facility equipped with wider diagnostic and curative capabilities. Pre-referral ARC is only effective as a life-saving commodity if followed promptly by this higher level of care. Among others, financial, geographical, and infrastructural barriers make the rapid transfer of (severely ill) patients challenging.

Objectives of this session on referral were to provide country specific challenges and opportunities around the referral of children with severe febrile illness, and contextualize experiences to allow countries to assess how these experiences may be applicable to their own situation.

Challenges and good practices

There may be low community awareness of the danger signs of severe malaria and the treatment options available at community level. In Uganda, there was an average delay of 2 days before reporting to any point of care (pharmacy, health facility or CHW), including those within the community itself (CARAMAL).

CHWs are not always engaged as a first point of care. CHWs are meant to be the first point of care in remote areas and responsible for administering ARC and initiating subsequent immediate referral. However, they can be insufficient in number and distribution, and inadequately supported, with functions that are not entirely clear to communities they serve. Since many work on a voluntary basis and are over-tasked, they cannot be expected to always be readily available.

Caramel findings were that in DRC, caretakers consulted CHW's in <10% of cases as a first point of care for their sick child, while in Nigeria, only 5% of all referrals seen in referral facilities came as a direct referral from CHW's and PHCs during the pre-ARC period. In Kole district, Uganda, 90% of providers identified CHWs as their first point of care. In Oyam and Kwania districts, only 54 and 41% respectively engaged CHWs first. At the community level, the focus should shift from knowledge dissemination to changing health seeking behaviour for severe malaria. As CHWs are an invaluable and lifesaving resource to communities and the health system, countries should move towards compensating them as accountable workers within the health system.[9]

Referral is often not completed. Infrastructural challenges and transport barriers exist in reaching referral facilities, especially during the rainy season. Some families cannot afford transport and must travel on foot. There are often no (functional) ambulances or a lack of other mean of transport provided by the health system. CARAMAL findings showed that in Uganda, 60% of patients referred by a CHW for severe malaria completed referral; in DRC, completion of referral was 65%. Over 80% of people in DRC have no means of transport, and the distance from communities to health facilities was >10 km away for 64% of severe malaria referrals by CHWs.

9. Compensation of CHWs is recommended by the WHO (2018), See WHO guideline on health policy and system support to optimize community health worker programmes, accessible via the following link: https://www.who.int/hrh/resources/health-policy-system-support-hw-programmes/en/. Recommendation 7 on remuneration.

To work around these challenges, emergency transport could be organized at community level. Successful pilots in Nigeria and Zambia involved volunteer drivers, supported by community funds. These volunteer drivers can also act as agents of change. Communities must actively participate in referral systems and organize around them, take ownership and be actively involved in developing strategies for emergency transport. Possible sustainable funding sources for emergency transport systems can include community based health insurance schemes. It became clear in discussions that referral is a multisectoral issue that must involve ministries of transport, infrastructure and digital communication. From the first level facility, transport should ideally be part of the formal health care services.

Costs of care at referral facilities can be high; in DRC, these were prohibitive for a majority of patients.

Long waiting times at referral facilities (due to overburdened staff and poor advance communication of referrals / triage upon arrival) puts patients at risk and reduces satisfaction with care. In these situations, setting up a digital communication chain (if sufficient coverage) and a referral protocol can be explored to help decrease waiting times.

Health seeking behaviour studies and known poor access to care point to *hidden mortality due to severe malaria* in communities. Operational research and death audits are needed to create a better understanding of actual severe malaria burden and mortality.

10. WHO bulletin from December 2019 Bull World Health Organ 2019;97:810–817| doi: http://dx.doi.org/10.2471/BLT.19.231506

Emergency transport models

Emergency Transport System in Nigeria

An existing EU-UNICEF partnership with the National Union of Road Transport Workers (NURTW), organizing locally available transport for maternal and new-born health, was extended to transportation of children referred with danger signs of severe malaria under CARAMAL. Under this scheme, through NURTW, volunteer drivers in communities receive various rewards for their services, such as provision of engine oil during Volunteers Appreciation Days, fuel vouchers, free vehicle servicing vouchers and cash vouchers linked to distances travelled, while in communities, transport loans with minimal interest are made available. The system proved highly effective in providing access to transportation, reducing costs of transport for families and improving referral completion for severe malaria.

Community based severe malaria referral system in Zambia

In Zambia, ARC was implemented in 5 districts following a successful pilot which included engagement and education of communities, training of CHW's and community grants for emergency transport systems involving bicycle ambulances with trained riders. 100% of severe malaria cases who received ARC from CHWs were successfully referred, and 72% travelled to the referral facility using the emergency transport system. The mortality from severe malaria was reduced by 96% in this pilot.[10]

Theme 4: ARC supply chain and stability guidance

Session objectives were to provide country specific findings on ARC distribution and storage, including challenges and opportunities, and provide an understanding of product characteristics related to ARC distribution and storage.

ARC 'melting'

The two WHO prequalified ARC formulations are identical softgel rectal capsules, packed in aluminium foil (alu/alu) blister packs which fully protect from humidity. These softgel capsules have a consistent thermostable shape. The soft gelatin shell is filled with a fatty matrix containing the artesunate drug which is designed to melt and release the drug at body temperature. However, outside the body, the softgel capsule is not affected and capsules can go through repeated cycles of melting and solidifying which does not damage either the inert fill or the capsule shell. The capsule can be returned to "solid" and used simply by cooling it, and can be safely used when the fill is in any physical state, although it is easier to insert the capsules when the fill is "solid".

As in communities, CHWs have reported that they discarded melted ARC, they have to be informed that the product can usually be re-solidified through cooling without reducing the effectiveness of the treatment.

ARC shelf life

The shelf life of the two WHO-prequalified generic ARCs is 24 months when stored at 25°C. The manufacturers both state that excursions above 30°C should be avoided.

In the WHO Public Assessment Report (WHOPAR), the WHO Prequalification Programme provides additional important recommendations on the storage of ARC: 'Artesunate suppositories are generally less stable above 30°C and in particular at the WHO accelerated storage condition (40°C/75%RH). To this end, procurers and distributors should take utmost care to avoid excursions above 30°C during storage and transportation of the product. However, it is understood that this storage requirement may not always be adhered to when the product is handled by community health workers (CHWs) located in areas where the ambient temperature is usually above 30°C. Therefore, procurers and distributors need to ensure that the product is distributed to CHWs located in such areas only as a short-term stock, generally not exceeding 4-6 months depending on the remaining shelf life of a given batch and severity of the ambient conditions where the batch is to be distributed.

If unused in the context of the CARAMAL project, ARC is retrieved after this period and disposed of – a practice that is neither resource-friendly nor sustainable.

Artesunate degrades over time and degradation is greater at higher temperatures. The degradation of artesunate encapsulated in ARCs is a slow process, as shown by the below ARC stability data, which were generated by the manufacturers from their registration stability batches (average values from all batches tested are presented).

Capsule Stability – Percent Artesunate Data

25°C – Generics and TDR

	3m	6m	9m	12m	18m	24m
	99%					95%

30°C

	3m	6m	9m	12m	18m	24m
Generic 1	99%				92%	NT
Generic 2	98%				94%	89%
TDR	96%					91%

40°C – Generics and TDR

3m	6m	9m	12m	18m	24m
99%	89%				

Each capsule must contain 90-105% of the claimed 100 mg artesunate during its shelf life. When stored at a consistent temperature of 30° for 24 months, the content is approximately 90% for both generic ARC products. One manufacturer did not test at 24 months (NT) due to borderline OoS value for a non-specified degradation product at the 18 months timepoint. At community level, temperatures fluctuate and are not consistently >30°C. The decrease in artesunate content is, therefore, likely to be less than in the above study. The manufacturers' stability data suggest that ARC stored in the field between 6 and 24 months is likely to be at a level that does not impact the clinical effectiveness of ARC, taking into account both variations in patient dosage introduced by the ARC age dosing regimen, and the naturally variable rectal absorption.

The CARAMAL project monitors temperatures in about 10 ARC storage sites per country for further analysis.

Storage solutions

Storage and handling of ARC in Uganda during the CARAMAL pilot project

In the context of CARAMAL, in health facilities in Uganda, ARC is kept on the lower shelves, away from the wall directly facing the sun. Where storerooms are small and the recorded temperatures are above 30°C, ARC is kept in a different secure and cool location outside the storeroom. ARC is issued in small stocks to CHWs during quarterly review meetings, for immediate transport back to their communities, avoiding direct body contact. Most CHWs store ARC in their grass thatched houses which are normally cooler than the outside environment. CHWs are instructed to keep ARC away from cooking areas, doors and windows. Furthermore, CHWs are instructed to transport ARC stocks from health facility to the community during early mornings or late afternoons, avoiding the heat of the day.

In Uganda, temperatures ranged from 28 to 36°C at the time of project inception. A decision was therefore made to retrieve ARC from communities every 3 months. This proved logistically complex and led to stock outs at community level as well as reduced confidence in this pre-referral intervention. Retrieving the commodity is neither a resource-friendly nor a sustainable option.

Novel storage ideas in a high temperature setting: an example from DRC

In DRC, temperatures during the hot and dry season exceed 30°C at the hottest time of day; storage solutions deployed were bamboo racks which allow for air flow, and a container sunk in a bucket of water in case of high temperatures (see picture below).

Challenges and good practices

Low quality, ineffective ARC formulations are available in some countries and undermine communities' trust in the effectiveness of ARC. Contrary to prequalified products, these formulations are not stable at high temperatures and may put lives at risk. Countries should be supported to ban low quality formulations of AS; strong guidance is needed from WHO and partners on the use of prequalified AS products, and where and how to procure and use these. WHO has issued an information note on rectal artesunate for pre-referral "treatment" of severe malaria; the information note is available under the following link: https://www.who.int/malaria/publications/atoz/rectal-artesunate-severe-malaria/en/.

Retrieving ARC from communities within 6 months is logistically challenging, costly, and risks stock outs and loss of trust at community level. Robust data and operational research are needed to demonstrate the stability of ARC under real field conditions, and pragmatic guidance is required for transportation storage of ARC, particularly at community level. Careful quantification and distribution should be exercised to avoid overstocking as well as stock outs and ensure uninterrupted availability.

CHWs receiving only small stocks of ARC may run out quickly, but cannot be expected to frequently travel to health facilities for refills. Temporary stock outs at community level can therefore easily occur. These stock outs can lead to poor satisfaction with CHW care and may negatively affect care-seeking behaviour. Moreover, misunderstandings about 'melting' of capsules may lead to these being wrongly discarded by CHW's. To this end, a guidance document with simplified storage and transportation guidelines for ARC, including education on ARC stability ('melting' is not a problem) should be created.

Concluding remarks

Effective strengthening of severe malaria systems requires not only funding and efforts to introduce the ARC commodity, but should have a holistic focus on all commodities and components along the continuum of care. This includes timely and feasible referral and ensuring the presence of higher-level facilities that can provide the appropriate standard of care. In the meeting, it became apparent that challenges in these aspects were similar across countries, and that more operational guidance in introducing and scaling up ARC within the cascade of care to manage severely ill children is necessary. The need for generating further stability data on ARC as well as better guidance on its storage and transportation were identified as a priority.

> "The need for generating further stability data on ARC as well as better guidance on its storage and transportation were identified as a priority."

The meeting was characterized by a very high level of engagement and motivation of both countries and partners. As a next step, countries are encouraged to develop concrete action plans for the next 12 months for the successful implementation of ARC and Inj AS, along the lines of the themes of the meeting: coordination, service delivery pre- and post-referral, referral, supply chain and surveillance.

In late 2020 or early 2021, a similar meeting may be organized with the aim to share final CARAMAL study results and discuss progress made in countries.

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Annex 1: Agenda and List of Participants

Agenda

Day 1 – October 21, 2019 – Intercorp Hilton, Level M2, Borno-Rivers Rooms

Chair and co-chair: Olugbenga Mokuolu, NMEP, Chair / Jackson Sillah, WHO AFRO, Co-chair

Time	Theme	Session	Speakers	Time needed
7:45 – 8:00		Registration		
8:00-8:15		Welcome and opening remarks	Bala Audu, National Coordinator, NMEP Nigeria	15 minutes
8:15-8:30		Objectives of the meeting	Jackson Sillah, WHO AFRO Co-chair	15 minutes
8:30-9:00	Setting the scene	Current guidelines for the treatment of severe malaria	Peter Olumese, WHO Geneva	10 minutes
		Severe malaria products	Hans Rietveld, MMV	10 minutes
		Roll out and uptake of Rectal Artesunate and Injectable Artesunate	Theodoor Visser, CHAI	10 minutes
9:00-9:05		Introduction of themes: 1. Coordination in funding and implementation 2. Service delivery pre- and post-referral 3. Referral 4. Logistics & supply chain management	Eliza Walwyn-Jones, CHAI	5 minutes
9:05-10:35	Theme 1: Coordination in funding and implementation **Moderator: Valentina Buj**	Nigeria:	Nnenna Ogbulafor, NMEP	15 minutes
		Uganda:	Denis Rubahika, NMCP	15 minutes
		DRC:	Rie Takesue - UNICEF/ DRC	15 minutes
		Remarks by severe malaria donors	Jordan Burns, PMI	15 minutes
		Discussion with presenters and audience		30 minutes
10:35-11:00		Coffee break		25 minutes
11:00-12:45	Theme 2: Service delivery pre- and post-referral **Moderator: Christian Lengeler**	Introduction to session	Christian Lengeler	10 minutes
		Preliminary learnings on pre- and post-referral care in CARAMAL countries	DRC: Antoinette Kitoto Tshefu Uganda: Phyllis Awor Nigeria: Ocheche Yusuf	30 minutes
		MMV rapid assessments of severe malaria case management: Uganda, DRC, Liberia	Hans Rietveld, MMV	15 minutes

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Day 1. Continued

		Understanding the role of and involving private sector providers	Alex Ogwal, CHAI Uganda	15 minutes
		Continuum of care for severe malaria from community to hospital	Martin de Smet, MSF	10 minutes
		Discussion with presenters and audience		25 minutes
12:45-1:45		Lunch		
1:45-3:00	Theme 3: Referral Moderator: Martin de Smet	Learnings from CARAMAL on seeking, reaching and receiving care	DRC: Antoinette Kitoto Tshefu Uganda: Phyllis Awor Nigeria: Ocheche Yusuf	30 minutes (10 mins/country)
		Accessible & affordable transport from community to referral facility: Emergency Transport System (ETS) in Nigeria	Halima Abdu, Bauchi Field Office, UNICEF	10 minutes
		Results and learnings from a community-based severe malaria pilot project in rural Zambia	Stephen Bwalya, Zambia NMCP	10 minutes
		Discussion with presenters and audience		25 minutes
3:00-3:30		Coffee break		30 minutes
3:30-4:45	Theme 4: Logistics and supply chain management Moderator: Hans Rietveld	Rectal Artesunate supply chain management: quantification, transport and storage	Valentina Buj presenting on behalf of Uganda UNICEF	15 mins
		Rectal Artesunate supply chain and stability guidance	Andrew Slade, MMV	20 minutes
		Novel storage ideas in a high temperature setting: An example from DRC	Alain Mugoto, DRC PNLP	10 minutes
		Discussion with presenters and audience		30 minutes
4:45-5:10		Summary of day 1 with key takeaways	Margriet den Boer, Rapporteur	25 minutes
5:10-5:15		Day 2 logistics	Eliza Walwyn-Jones	5 minutes
5:15-5:30		Closing	Chair	15 minutes

Day 2 – October 22, 2019 – Intercorp Hilton Hotel, Level M2, Borno-Rivers Rooms			
Time	**Session**	**Speakers**	**Time needed**
8:30-8:50	Day 1 Recap	Rapporteur	20 minutes
8:50-9:00	Introduction to break out sessions and reporting template	Eliza Walwyn-Jones, CHAI	10 minutes
9:00-10:30	Country breakout sessions: Rotations through 3 / 5 thematic stations (30 minutes each)		90 minutes
10:30-11:00	Coffee break		30 minutes
11:00-12:30	Breakout sessions, continued: Rotations through 5 / 5 thematic stations (30 minutes each)		90 minutes
12:30- 2:00	Lunch		90 minutes
2:00-4:00	Country presentations to group on action plan broken down by thematic areas		2 hours
4:00-4:30	Break		30 minutes
4:30-4:50	Summary of day 2 with key takeaways	Rapporteur	20 minutes
4:50-5:00	Closing	Chair	10 minutes

List of Participants

Halima	**Abdu**	Nigeria	UNICEF
Adebimpe	**Adebiyi**	Nigeria	Child Health Division
Isaac	**Adejo**	Nigeria	MSH
Bosede	**Adeniran**	Nigeria	Child Health Division
Issa	**Amadou**	Niger	NMCP
Maureen	**Amutuhaire**	Uganda	NMCP
Joselyn	**Atuhairwe**	Nigeria	CHAI
Bala Mohamed	**Audu**	Nigeria	NMCP
Phyllis	**Awor**	Uganda	Makerere University
Patrick	**Bahizi Bizoza**	DRC	WHO
Joel Naa	**Balbaare**	Ghana	Global Fund
Philippe	**Batienon**	Senegal	RBM
Sanjana	**Bhardwaj**	Nigeria	UNICEF
Valentina	**Buj**	Switzerland	UNICEF
Jordan	**Burns**	USA	PMI
Stephen	**Bwalya**	Zambia	NMCP
Mugoto	**Byamungu**	DRC	MOH
Yakubu	**Cherima**	Nigeria	Malaria Consortium

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List of Participants. Continued

Welby	**Chimwani**	Kenya	NMCP
Martin	**De Smet**	Belgium	MSF
Clifford	**Dedza**	Malawi	NMCP
Margriet	**den Boer**	UK	rapporteur
Patience	**Dhliwayo**	Zimbabwe	NMCP
Mércia	**Dimene**	Mozambique	NMCP
Amadou	**Doucoure**	Senegal	PNLP
Stephan	**Duparc**	Switzerland	MMV
Perpetua	**Egonmwan**	Nigeria	NMEP
Keith	**Esch**	USA	PMI
Sonachi	**Ezeiru**	Nigeria	CRS
Bosede	**Ezekwe**	Nigeria	FMOH
Chizoba	**Fashanu**	Nigeria	CHAI
Dale	**Halliday**	Switzerland	Unitaid
Theotime	**Migan**	Benin	NMCP
Uwem	**Inyang**	Nigeria	PMI USAID
Olusesan	**Ishola-Gbenla**	Nigeria	Management Sciences for Health
Mina	**Jaja**	Nigeria	NMEP
Anitta	**Kamara**	Sierra Leone	NMCP
Madina	**Konate Coulibaly**	Mali	NMCP
Oumar	**Kone**	Mali	PNLP
Sosten	**Lankhulani**	Malawi	NMCP
Christian	**Lengeler**	Switzerland	Swiss TPH
Christopher	**Lourenço**	USA	PSI
Mark	**Maire**	Nigeria	PMI / CDC
Momolou	**Massaquoi**	Liberia	MOH
Anita	**Mbadiwe**	Nigeria	CHAI
Elisa	**Miguel**	Angola	NMCP
Wahjib	**Mohammed**	Ghana	NMCP
Olugbenga	**Mokuolu**	Nigeria	NMEP
Inocencia	**Morais**	Angola	NMCP
Salou	**Mounkaila**	Niger	NMCP
Eric	**Mukomena Sompwe**	DRC	PNLP
Filipe	**Murimirgua**	Mozambique	NMCP
Monique	**Murindahabi Ruyange**	Burkina Faso	RBM
Ombeni	**Mwerindeo**	Switzerland	Unitaid
Andriamananjara Mauricette	**Nambinisoa**	Madagascar	NMCP
Christophe	**Ndoua**	CAR	PNLP
Linda	**Nsahtime-Akondeng**	Nigeria	UNICEF
Timothy	**Obot**	Nigeria	NMEP
Dorothy	**Ochola-Odongo**	Nigeria	UNICEF
Nnena	**Ogbulafor**	Nigeria	NMEP
Alex	**Ogwal**	Uganda	CHAI
Abraham	**Okita**	Nigeria	CHAI
Placide	**Welo Okitayemba**	DRC	iCCM Program
Charles	**Okon**	Nigeria	Akena
Tayo	**Olaleye**	Nigeria	CHAI
Carine	**Olinga**	DRC	CHAI

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List of Participants. Continued

Peter	**Olumese**	Switzerland	WHO
Omokore	**Oluseyi**	Nigeria	FMOH
Femi	**Owoeye**	Nigeria	BMGF
Frederic Pinguedbamba	**Dianda**	Burkina Faso	NMCP
Oliver	**Pratt**	Liberia	NMCP
Abigail	**Pratt**	USA	BMGF
Tiana	**Ramanatiaray**	Madagascar	NMCP
Voahangy	**Razanakotomalala**	Madagascar	NMCP
Remi	**Peregrino**	Nigeria	CHAI
Hans	**Rietveld**	Switzerland	MMV
Denis	**Rubahika**	Uganda	NMCP
John Hafu	**Sande**	Malawi	NMCP
Vincent	**Sanogo**	Mali	MOH
Yacouba	**Savadogo**	Burkina Faso	NMCP
Silvia	**Schwarte**	Switzerland	WHO
Emmanuel	**Shekarau**	Nigeria	NMEP
Jackson	**Sillah**	Congo (Republic)	WHO / AFRO
Andrew	**Slade**	Switzerland	MMV
Laura	**Steinhardt**	Nigeria	CDCP
Rie	**Takesue**	DRC	UNICEF
Tinu	**Taylor**	Nigeria	FMOH
Jose	**Tchofa**	Nigeria	PMI
Soukeynatou	**Traore**	Nigeria	Management Sciences for Health
Andritiana	**Tsarafihavy**	Madagascar	PMI Access
Antoinette Kitoto	**Tshefu**	DRC	Kinshasa School of Public Health
Alhaji S	**Turay**	Sierra Leone	MOH
Joy	**Ufere**	Nigeria	WHO
Essien	**Ukanna**	Switzerland	Unitaid
Theodoor	**Visser**	USA	CHAI
Paul	**Waibale**	Liberia	Management Sciences for Health
Eliza	**Walwyn-Jones**	Botswana	CHAI
S. Olasford	**Wiah**	Liberia	CHSD
Bélia	**Xirinda**	Mozambique	NMCP
Ambachew	**Yohannes**	Switzerland	Unitaid
Ocheche	**Yusuf**	Nigeria	Akena

Annex 2: Pre-meeting Questionnaire

Interviewee Name and Function: .....

Country: .....

Date of interview: .....

Personal role in severe malaria case management: .....

Interview administered by: .....

Pre-meeting survey for severe malaria case management implementation experience

#	Theme	Topic	Are you interested hearing from colleagues with experiences in this topic/ aspect? 1. Low interest 2. Modest interest 3. High interest	Are there experiences in your country that would be relevant to share with other countries related to this topic/ aspect?	If yes provide contact details of resource persons or agencies which has relevant experience to share on this topic	Comment
			(Note 1, 2 or 3)	(Note Yes/No)	(Name, Function, phone or email)	
1	Coordination	How to deal with multiple actors, funding streams, supply lines and implementing agencies				
2		How to harmonize NMCP, child health/community health programs, pharmacy departments, and their policies/ guidelines				
3	Supply Chain Management	How to adequately conduct quantification, forecasting, and ordering of rectal artesunate and/or injectable artesunate				
4		How to handle storage, transport, replacement of unused rectal artesunate, and routine replenishment				
5		How to handle transport and storage of rectal artesunate when exposed to temperatures of 35-40 °C or higher				
6	Behavior & Communication	How to build awareness on signs of severe disease among parents/caretakers; how to promote appropriate care seeking behaviors				
7		How to overcome reluctance/poor acceptability of rectal artesunate by parents/caretakers				
8	Referral	How to ensure accessible & affordable transport from community to referral facility following administration of rectal artesunate				
9	Service Delivery	How to involve informal and private providers (i.e., traditional healers, private sector) in early recognition of severe febrile illnesses and prompt referral				
10		How to ensure knowledge, skills and adherence to guidance for diagnosis, treatment and referral by Community Health Workers and/or PHC providers				
11		How to monitor appropriate case management practices with rectal artesunate (i.e., appropriately administration to correct patients)				
12		How to promote and monitor complete post-referral treatment with injectable artesunate (instead of quinine) and full course of ACT at referral facility level, including appropriate case management for special groups (e.g. pregnant women)				