Severe Malaria Global Stakeholder Meeting

8-9 February 2022

Defeating Malaria Together

MMV
Medicines for Malaria Venture

Abbreviations

ACT	Artemisinin-based combination therapy
AL	Artemether/lumefantrine
CARAMAL	Community Access to Rectal Artesunate for Malaria
CHAI	Clinton Health Access Initiative
CHW	Community health worker
GFATM	Global Fund to Fight AIDS TB and Malaria
iCCM	Integrated community case management
Inj AS	Injectable artesunate
KSPH	Kinshasa School of Public Health
MMV	Medicines for Malaria Venture
MSF	Médecins Sans Frontières
NMCP	National Malaria Control Program
PHC	Primary healthcare centre
RBM	Roll Back Malaria Partnership to End Malaria
PMI	United States President's Malaria Initiative
RAS	Rectal artesunate or artesunate rectal capsules (ARC)
SBCC	Social and Behaviour Change Communication
Swiss TPH	Swiss Tropical and Public Health Institute
VHT	Village health team
WHO	World Health Organization

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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 Partnership Case Management Working Group and in collaboration with WHO, PMI and GFATM, with input from the Community Access to Rectal Artesunate for Malaria[1] (CARAMAL) team. The meeting was funded by Unitaid. Co-chairs were Prof. Olugbenga Mokuolu and Dr Elizabeth Chizema.

The meeting was held virtually and took place on the afternoons of the 8th and 9th of February, 2022.

The first Severe Malaria Global Stakeholder Meeting was held in Abuja, Nigeria, in 2019[2] and assembled African countries that had recently commenced the rollout of rectal artesunate (RAS). The meeting built on stakeholder meetings focused on injectable artesunate (Inj AS) and RAS held in 2011 and 2016, respectively[3,4]. This second meeting offered a platform for sharing experiences of the recent wide-scale deployment of RAS in Africa. It also served as a forum to disseminate lessons learnt from operational research projects such as CARAMAL and other pilots and experiences in implementing RAS, and it offered an opportunity to discuss and analyse WHO's guidance on the use of RAS.

The meeting brought together National Malaria Control Programs (NMCPs), Ministry of Health units involved in iCCM, research institutions investing in RAS operational research or with expertise in assessment of observational studies, donors in the malaria space and technical agencies. Delegations from 35 malaria-endemic countries were in attendance: Angola, Benin, Burkina Faso, Cabo Verde, Cameroun, Comoros, Congo, Côte d'Ivoire, Djibouti, DRC, Eswatini, Ethiopia, Ghana, Guinea, Guinea Bissau, Guyana, Kenya, Liberia, Madagascar, Malawi, Mauritania, Mozambique, Namibia, Niger, Nigeria, Pakistan, São Tomé & Príncipe, Senegal, Sierra Leone, Somalia, Sudan, Togo, Uganda, Zambia and Zimbabwe.

In addition, the following organizations and projects were represented: Akena Associates, African Leaders Malaria Alliance, Breakthrough Action, CDC, Chemonics, GFATM, Impact Malaria, Imperial College, Jhpiego, Kinshasa School of Public Health, LSHTM, Makerere University, Management Sciences for Health, Mentor Initiative, MSF, PSI, RBM Partnership to End Malaria, Swiss TPH, Transaid, UNDP, UNICEF, Unitaid, University of Cape Town, US PMI, Village Reach, WHO and World Vision.

1. The 3-year CARAMAL project, implemented by the Clinton Health Access Initiative (CHAI), UNICEF, and the Swiss Tropical and Public Health Institute (Swiss TPH) provided artesunate rectal capsules as a pre-referral intervention for severe malaria patients. It had two major components: the pilot implementation of RAS in selected areas of the Democratic Republic of the Congo (DRC), Nigeria and Uganda, and operational research on the introduction of RAS into established integrated community case management (iCCM) platforms.
2. https://www.severe-malaria.org/resources/severe-malaria-stakeholder-meeting-21-22-october-2019-abuja
3. https://www.severemalaria.org/sites/mmv-smo/files/content/attachments/2017-01-27/Injectable_Artesunate_Stakeholders_Meeting_Report_3.pdf
4. https://www.mmv.org/newsroom/publications/rectal-artesunate-stakeholders-meeting-report

Aims and objectives

The main objectives of the meeting were: (a) to inform the malaria community, specifically NMCPs, on the latest information/evidence regarding the use and uptake of RAS in the context of strengthening case management of children with severe malaria; and (b) to discuss implications for operational guidance and scale up plans of RAS.

The ultimate goal of the meeting was to identify the best way forward for the implementation of RAS in order to achieve a better quality of care and thus, reduced mortality from severe malaria.

The meeting sessions

Day 1

The meeting began with a short review of the adoption of WHO guidelines and the uptake of current severe malaria commodities in Africa. This was followed by a summary of the findings of the CARAMAL studies, insights from the patient journey market research by MMV, and countries' experiences and lessons learnt in rolling out RAS in communities in Uganda, Sierra Leone, Senegal, DRC, Nigeria and Zambia. The meeting concluded with a panel discussion on the management of febrile children along the continuum of care.

Day 2

The day started with an overview of the current evidence of artemisinin partial resistance in Africa. The WHO presented its latest severe malaria guidance and PMI, GFATM and MMV gave an overview of the implications for procurement and supply chain. This was followed by a panel discussion on strengthening primary health care, including community health. Afterwards, country representatives were given time to formulate questions which were answered by the relevant experts and organizations.

Meeting conclusion

The meeting concluded with an agreement on the way forward endorsed by all stakeholders. There was a general agreement that the evidence generated by the CARAMAL project — no reduction of child mortality after implementation of RAS — should trigger countries to ensure strict adherence to WHO guidelines to ensure the correct use of RAS as a pre-referral intervention, including:

1. (correct) diagnosis and administration of RAS;
2. immediate referral; and
3. complete treatment with at least 24 hours of injectable artesunate and a three-day ACT.

Introduction

Malaria remains one of the leading causes of illness and death in children under 5 years of age. The heaviest malaria burden is in sub-Saharan African countries, which accounted for an estimated 95% of malaria cases and 96% of malaria deaths in 2020[5].

Malaria can result in a wide variety of symptoms, ranging from absent or mild symptoms such as a headache or 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. If not treated, mortality due to severe malaria, particularly cerebral malaria approaches 100%. With prompt, effective treatment and supportive care, this severe malaria rate falls to 10–20%, depending on available care[6].

Patients with severe malaria should first be treated with injectable (intramuscular or intravenous) artesunate for at least 24 hours and until they can tolerate oral medication. At that time, the patient should complete treatment with three days of oral artemisinin-based combination therapy (ACT). If Inj AS 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 health facilities. In such settings, many factors 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 Inj AS is not readily available, RAS can be an effective pre-referral intervention for young children under 6 years of age[7]. RAS rapidly clears (i.e., within 24 hours) 90% or more of the malaria parasites. Its impact on mortality as a pre-referral intervention for severe malaria was evaluated in a single large individual randomized placebo-controlled trial (2009) involving 17,826 children and adults in Bangladesh, Ghana and the United Republic of Tanzania, in which pre-referral RAS was compared with placebo, followed by quinine parenteral treatment at referral hospital levels. Used this way, RAS reduced mortality by approximately 25% in children <6 years but was associated with higher mortality in adults[8]. To date, 14 randomized controlled clinical trials have been conducted documenting the safety, tolerability, efficacy and pharmacological characteristics of RAS[9].

As a pre-referral intervention option for severe malaria, RAS administration must be followed by immediate transfer to an appropriate facility for intensive nursing care and treatment with Inj AS for at least 24 hours followed by a full 3-day ACT treatment, once the patient can tolerate oral medication[10].

In 2020, an estimated 627,000 people died from malaria globally, 77% of whom were children under 5 years of age living in Africa. These children all died of severe malaria. Despite WHO recommendations the use of RAS and Inj AS in Africa remained fairly stagnant over the first 5–10 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 (30 mg, 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, both CIPLA and Strides have 100 mg products which received prequalification in 2018. About 20 countries have already started using RAS, and others are poised to scale-up the 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. Between 2018 and 2020, approximately 3 million WHO-prequalified RAS capsules were procured by more than 20 countries. The six countries with the largest cumulative volumes of RAS procurement were DRC, Senegal, South Sudan, Angola, Niger and Ethiopia. Of the 44 malaria-endemic countries in Africa, 22 have national guidelines for the treatment of malaria which are aligned with WHO guidance on RAS and Inj AS implementation.

5. World Malaria Report 2021, https://www.who.int/publications/i/item/9789240040496
6. WHO Guidelines for Malaria, 13 July 2021, https://www.who.int/publications/i/item/guidelines-for-malaria
7. WHO Guidelines for Malaria, 13 July 2021, https://www.who.int/publications/i/item/guidelines-for-malaria
8. 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
9. 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.
10. Guidelines for treatment of malaria, WHO, 3rd Edition (2015)

Significant challenges remain. RAS is a pre-referral intervention intended for use in children under 6 years of age at the peripheral level as part of a continuum of care that includes referral and definitive case management with Inj AS and 3 days of oral ACTs 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. But many of the countries where the product may have a significant impact on malaria mortality have weak or non-existent iCCM platforms, substantial and persistent referral barriers, inadequate management of severe malaria at the hospital level and/or inadequate post-referral care. A recent landscape assessment[11] found that even in countries where national guidelines align with WHO guidelines, many countries did not have community-based health services to deliver RAS as part of a functional continuum 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.

To inform strategies for RAS implementation and scale-up based on use in real-life settings, Unitaid invested in the CARAMAL project (Community Access to Rectal Artesunate for Malaria), a 3-year operational research project (2018–2020). It aimed to reduce malaria mortality in children by improving the community management of suspected severe malaria and to advance the development of operational guidance for the scale-up of pre-referral RAS for severe malaria. The project relied on two components: the pilot implementation of RAS in integrated community case management (iCCM) networks in selected areas of the DRC, Nigeria and Uganda, and operational research on the introduction of RAS into established iCCM platforms.

Study findings demonstrated low treatment seeking at iCCM networks, and poor referral completion. Post-referral treatment was often incomplete and, in particular, the required 3-day ACT was not consistently administered, leaving patients with RAS/Inj AS receiving artemisinin monotherapy[12]. No overall positive effect on case fatality rate (CFR) of severe malaria could be demonstrated.

Following these results, the WHO issued the following information note in January 2022[13]:

- 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.

This meeting offered the opportunity for countries and stakeholders to reflect on and further discuss this guidance and share results and lessons learnt from operational research projects such as CARAMAL and other pilots, studies and implementation experiences since 2019.

A complete agenda can be found in Annex 1. Many questions were asked during the meeting and not all could be answered. In Annex 2, answers to all the questions can be found.

11. CHAI conducted a landscape assessment of rectal artesunate (ARC) procurement and use as part of Output 4 in 2018
12. 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
13. WHO Information Note, January 2022, https://apps.who.int/iris/handle/10665/351187

CARAMAL study findings and interpretation

The CARAMAL project was a large-scale observational study conducted between 2018 and 2020. It aimed to assess the impact of quality controlled pre-referral RAS implemented under real-world conditions through community-based health care providers. The study was conducted in remote settings with a high malaria endemicity in the DRC, Nigeria and Uganda. Only minimal supportive interventions like provision of Inj AS to referral health centres in DRC, implementation of two-way referral slips and extension of an existing emergency transport system in Nigeria and support from district-level coordinators in data collection and RAS supply in Uganda were implemented. 13,758 children below 5 years of age presenting to a community-based health provider with a positive malaria test and signs of severe malaria were enrolled and followed up during referral, admission and after 28 days to assess the treatment applied and the child's health status. In parallel, cross-sectional surveys of households and health care providers within the study area were performed, as well as artemisinin resistance and cost studies. The analysis of findings was based on an overall before-and-after study design, with an individual RAS user versus non-user analysis.

It should be noted that the results of this observational study have not yet been published in any peer reviewed journal; they were, however, presented by members of the CARAMAL study team.

Results are as follows:

- Acceptability and uptake among health workers was good. Uptake varied from mostly high (DRC, Uganda) to variable over the study period (Nigeria). RAS was administered to 88% of eligible patients in the DRC (RAS was also introduced at PHC level), 52% in Nigeria, and 70% in Uganda. Administration was primarily a function of availability of the product.
- Treatment compliance with Inj AS followed by administration of an oral ACT in referral facilities was rather poor, ranging from 76% of children in DRC, to 45% in Uganda and only 1% in Nigeria. Taking into account both in-hospital ACT administration plus discharge prescriptions, ACT provision was 77% in DRC, 97% in Uganda and 46% in Nigeria. Overall, 42% of the children enrolled completed the full course of severe malaria treatment with Inj AS and an ACT.
- No overall positive effect on CFR following the introduction of RAS was found in the before-and-after study analysis. The CFR evaluated at 28 days was higher in Nigeria and DRC after the roll-out of RAS and slightly lower in Uganda (post-RAS vs. pre-RAS: 7.0 vs. 5.7% in the DRC, 19.7 vs 7.7% in Nigeria, 0.4 vs 0.6% in Uganda).
- In an individual analysis of users versus non-users of RAS, RAS was found to reduce the risk of being dead or sick after 28 days in Uganda while no positive effect was found in DRC and Nigeria.
- RAS administration was associated with a reduced likelihood of completing referral to an appropriate higher-level health facility among children attending a Primary Health Care (PHC) facility in Nigeria. Additionally, there was evidence of an association between RAS administration and lower referral completion in DRC.
- Information on RAS compliance was collected for 1,107 children. Compliance in children < 3 years old (dose: one RAS capsule) was high, however in children ≥ 3 years (dose: two RAS capsules), RAS was under-dosed in a large proportion of children (14% in DRC, 68% in Nigeria, 42% in Uganda).
- Stock out of RAS was a frequently encountered problem, especially in DRC.

These results must be interpreted with care; there were biases, confounders and large differences between the three countries.

- The health systems in the three countries are set up differently. In Uganda, RAS was administered via the village health teams (VHTs) which consist of two community health workers (CHWs). There were 3,893 CHWs in the research area. In DRC, there were fewer CHWs (164 in the research area) and RAS was administered predominantly in primary health care (PHC) facilities. Compared to Uganda, in Nigeria and DRC the study took place in underserved areas with poor functional health systems and populations severely affected by poverty. Compared to the other two countries, in Nigeria RAS was often not used due to programmatic and supply issues. It was also observed that ACT usage was low in Nigeria before as well as after RAS implementation.
- CHWs were often given only small numbers of RAS capsules at any one time. Interruption of stock in case of high patient numbers is likely in this case. This may have influenced whether they were able and willing to offer the full dose to children.
- The distance from communities to health facilities in Uganda was generally less than 15 minutes whereas in the DRC and Nigeria it was often more than several hours. Malaria and other childhood diseases are highly endemic in these areas, and caregivers have to make numerous decisions on care-seeking for their children. Malaria episodes occur frequently, and often families cannot afford the transport fees to referral facilities. Caregivers may also decide to forego a visit as stock outs and absence of personnel are regular occurrences in health facilities, and there is subsequently a lack of trust that appropriate care will be given.

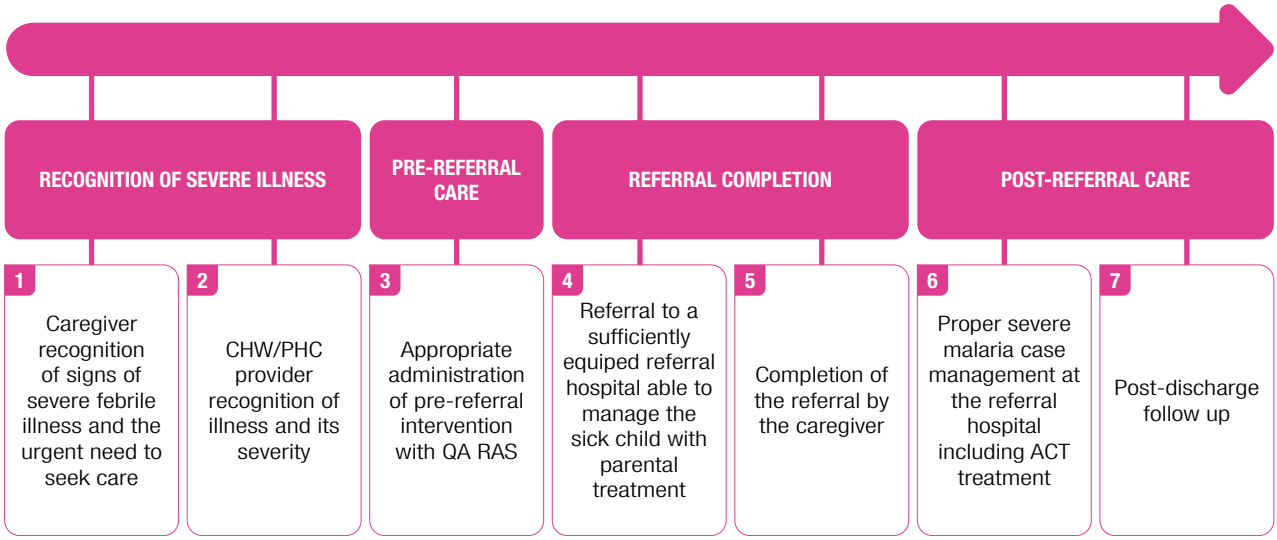
The CARAMAL project highlighted many challenges and deficiencies along the continuum of care, revealing health system weaknesses and inadequate quality of care. The results demonstrate that it is not sufficient to distribute RAS in underserved areas without addressing these challenges. The absence of trend monitoring in non-intervention areas makes it difficult to fully interpret the impact of other factors on changing CFR and critical study outcomes. This will be the next crucial step in improving quality of care and clinical outcomes of severe malaria.

Country experiences in implementation of RAS: challenges and key success factors

Presented by representatives from Uganda, Sierra Leone, Senegal, DRC, Nigeria and Zambia

Countries were requested to present on different aspects of the continuum of care, as shown below (Figure 1)

Figure 1: Stages of the continuum of care for a severely febrile child



Uganda: pre-referral care

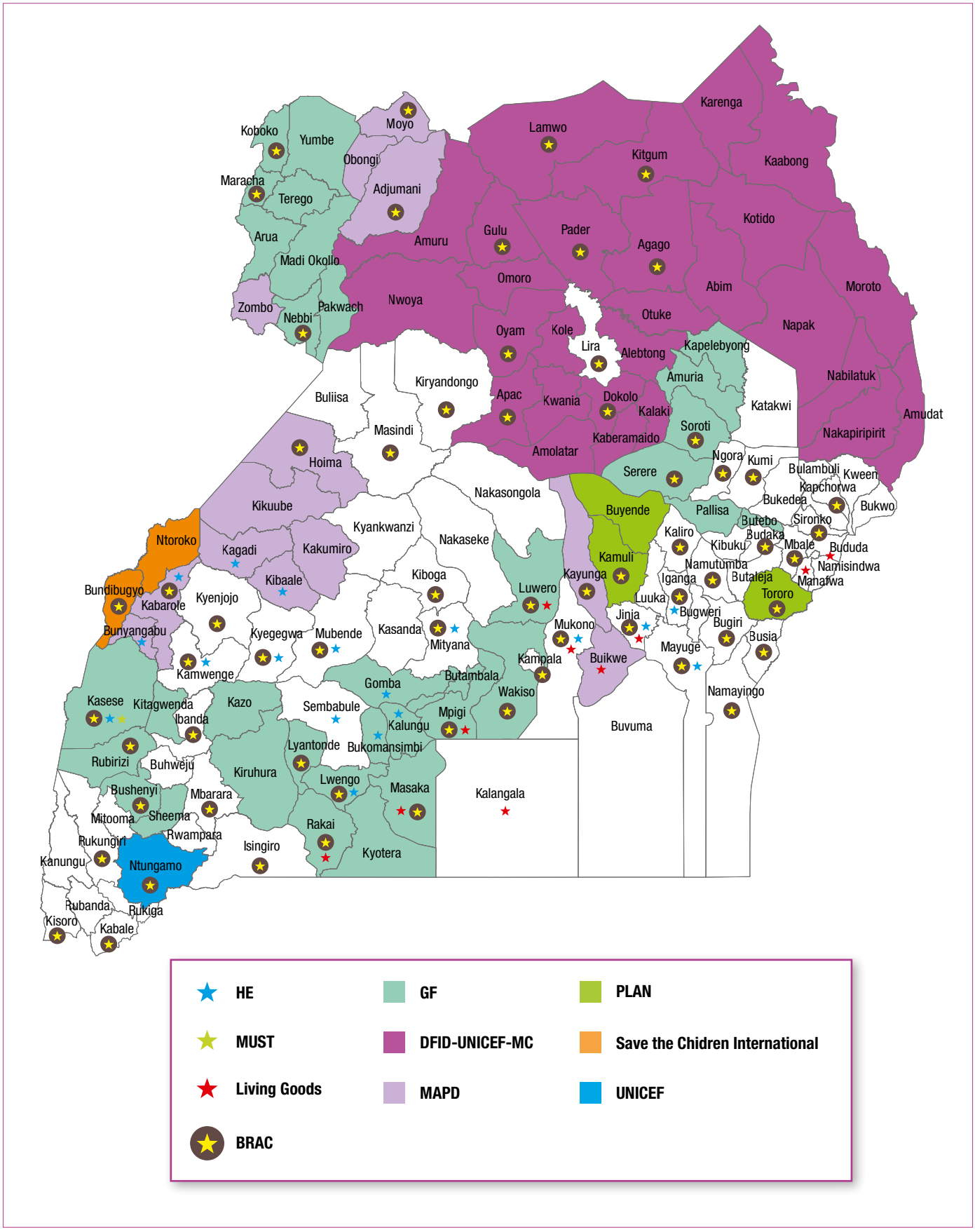
Introducing pre-referral RAS at community level and reflections on key supportive interventions essential to successfully integrate RAS into existing iCCM systems

In Uganda, iCCM is implemented in 70 districts, supported by different organizations (see Figure 2). RAS was delivered through the iCCM platform to children below 5 years of age at community level, and to children below 6 years of age at health centre II levels and where treatment for severe malaria is not available. RAS was procured by GFATM and the National Medical System schedules were utilized for last mile delivery, alongside other commodities, although there were some distribution delays due to innovations being introduced into the National Medical System. RAS was included in the iCCM and IMM guidelines, and information on RAS was included in Social and Behaviour Change Communication (SBCC). Mortality and clinical audits were done to improve severe malaria management.

Various challenges were encountered. RAS SBCC material was inadequate and since iCCM is not fully rolled out, training on RAS was not given across the entire country. In the future, support for SBCC materials for RAS is planned, as well as intensified communication on RAS. Refresher trainings are now ongoing across the country, leveraging on other case management trainings.

Incomplete referrals occurred for some of the children, thought to be due to full recoveries after RAS administration. Expiry of RAS stocks at village health team (VHT) level happened frequently and continuous mentorship and coaching was required to avoid this. During CARAMAL, a lesson learnt was that making parish coordinators part of the supervision structure delivering RAS to the VHTs supported stronger supply chain and commodity security at community level, thereby reducing expiries.

Figure 2: ICCM coverage in Uganda



Sierra Leone: referral completion

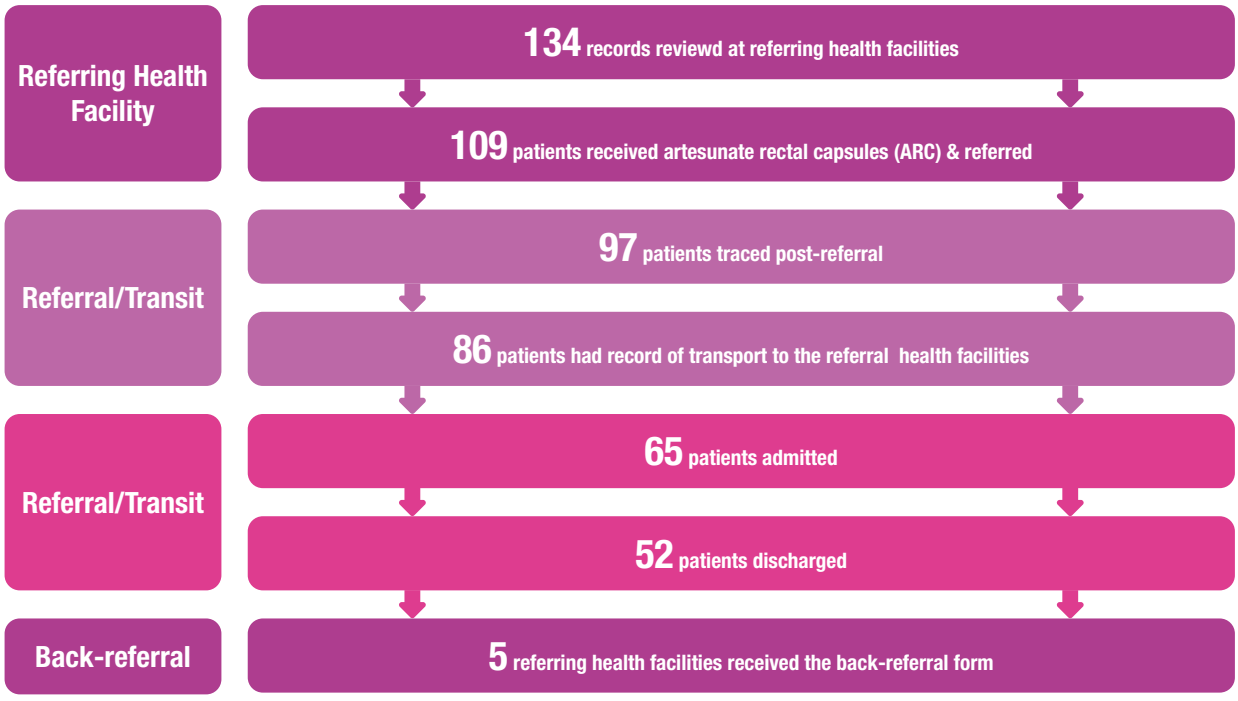
Introducing pre-referral RAS at the peripheral level and reflections on challenges with RAS introduction and efforts to ensure successful referral completion from community to hospital level

In 2019, PMI supported the Sierra Leone NMCP to procure its first supply of RAS for national rollout in 2020. Nationwide trainings (danger sign recognition, RAS administration, effective referral and reporting best practices) were conducted and RAS commodities were supplied to 2,452 providers across 14 districts.

A rapid assessment took place in 2020, supported by PMI, in which health outcomes of patients receiving pre-referral intervention were documented and a review of 134 records of patient journeys along the continuum of care was performed (Figure 3). The record reviews showed that approximately 96% of referral forms made it to the referral facility, but only 7% made it back to the referring facility.

The study looked at whether the proximity between referring facility and referral hospital explained death rates. They found that distance between the two facilities in this context did not affect death rates.

Figure 3 Record review of patient journeys along the severe malaria continuum of care



An ambulance system was responsible for 75% of referral transports, and should be bolstered. All deaths were reviewed and 50% occurred in facilities at a distance of at least 45 km from the district hospital. However, deaths due to late presentation also occurred in patients reaching health facilities within a short time.

Caretakers refused to proceed along the referral pathway in 11% of referred cases which indicates the need to create demand and to educate caretakers while addressing barriers to adhere to referral advice. Other challenges included delayed supplies of RAS leading to stock outs, and a lack of hospital staff trained to manage severe malaria cases.

Senegal: recognition of severe illness

The role of CHWs in the severe malaria continuum of care

In 2020, RAS was implemented in 2,218 villages in 35 districts with the highest malaria incidence in the country, and 3,096 doses of RAS were given to CHWs. Under the *Prise en Charge à Domicile program* (PECADOM Plus), in villages with difficult access to health services, 2,218 literate CHWs were selected by their communities, trained and regularly supervised. Their activities included active case detection via weekly sweeps, performed during the high malaria transmission season (for which they were incentivized by a small stipend), early malaria diagnosis and treatment, referral of severe cases and administration of RAS to children under 5 years of age with danger signs of severe malaria. This, combined with seasonal malaria prevention led to a decrease of severe malaria of 66% and a reduction in mortality from 158 to 93 cases between 2015 and 2020.

Lessons learnt include community mobilization efforts are key to quickly identifying symptomatic cases, and that the payment of a small stipend for active case detection is crucial for the motivation of CHWs. The intervention was well suited to areas with difficult access to health services and high levels of poverty. A challenge was that at community level, problems of transport to the referral facilities often arose.

DRC: recognition of severe illness, pre-referral care, referral completion and post-referral care

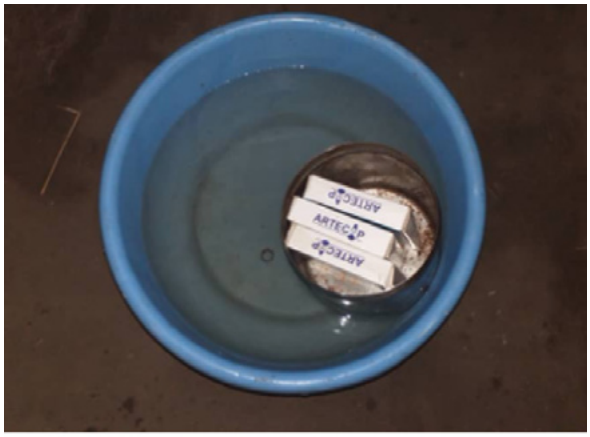
Experience with the use of RAS, Inj AS and ACTs in severe malaria patients in parts of rural DRC

A case was reviewed of an infant boy of 11 months old living in a village in Zone Santé of Kingandu, presenting with fever, refusal to breastfeed, apathy and vomiting. The child was brought to a community clinic where a rapid diagnostic test confirmed malaria. RAS was immediately administered by the nurse who then referred the child to a hospital 50 km away. The parents walked the first 15 km and then found a motorcycle to transport them to the hospital. Prior to arrival at the hospital the child began showing signs of improvement. After arrival at the hospital, he received 3 doses of Inj AS and recovered completely over a period of 7 days. The child successfully completed the referral chain with a full course of ACT back in his community and tested negative with a rapid diagnostic test (RDT) on day 28.

RAS was successfully deployed with good community participation during an outbreak in 4 Aires de Santé within the Zone Santé of Mukedi. Of 1,093 children below 5 years of age diagnosed with severe malaria, 924 received RAS and were referred to a health facility where they subsequently received Inj AS. Of these, 881 children were referred home with an ACT, and 43 received ACT in the health facility. As a result, malaria morbidity and mortality during this outbreak remained low — among 1,093 cases in 4 Aires de Santé, there were 26 deaths (2.4%).

Storage solutions

Some innovative approaches for RAS storage were used at community level, including storing RAS in mud houses in which the ambient temperature generally remains low during the hottest periods of the year, transporting RAS during evenings, and storing RAS in a container placed in a bucket of water.



Nigeria: post-referral care

How severely ill children, particularly those diagnosed with severe malaria are managed upon arrival in the hospital, and how initiatives like the quality of care work in Kano state has or will improve health outcomes

In 2020, cross-sectional surveys in Kano state showed that only 64% of severe malaria cases were treated according to the guidelines; the use of Inj AS for confirmed severe malaria patients was suboptimal (60%); 98% of CHWs had never used RAS and only 4.4% of positive patients with severe malaria were treated with recommended oral ACT as a follow-up. Many challenges were identified in the continuum of care, of which the most important was late care and referral seeking, and an inability to pay for treatments, which led to a high mortality amongst hospitalised severe malaria cases. Severe malaria patients are usually admitted 5 to 7 days after the onset of symptoms due to inappropriate care seeking in the private sector, or due to caretakers resorting to traditional medicine. There was also a higher focus on maternal health services in the emergency system than on children under 5 years of age, which affected timely referrals.

Before referral, most patients were given either intramuscular artemether or artemether/lumefantrine as pre-referral intervention. Inj AS and RAS are not commonly used due to high cost and/or lack of availability. Most patients received a malaria diagnostic test prior to admission/treatment initiation which could lead to delays in treatment initiation. At discharge, most providers scheduled patients for a post-treatment malaria parasitological test to be performed within 2 weeks. Few patients returned for post-treatment appointments.

The SMEP in Kano is supported by CHAI to improve case management through strengthening quality of care and data use. Interventions were implemented in two areas where a baseline survey showed that only 64% of the severe malaria cases were treated according to the guidelines and that there were challenges with data collection, review and use. The interventions focus on improving coordination with the state quality of care strategy, building up health worker capacity and development of key malaria data dashboards.

Practical lessons were learnt including the deployment of a peer-led learning approach as an effective and efficient way of building CHW capacity. This addresses high attrition rates and facility-level mentoring. The use of facility teams for malaria case management and monthly clinical meetings in secondary health facilities can improve adherence to treatment protocols and improve treatment outcomes.

Zambia: recognition of severe illness and pre-referral care

Results and learnings from a community-based severe malaria project in rural Zambia

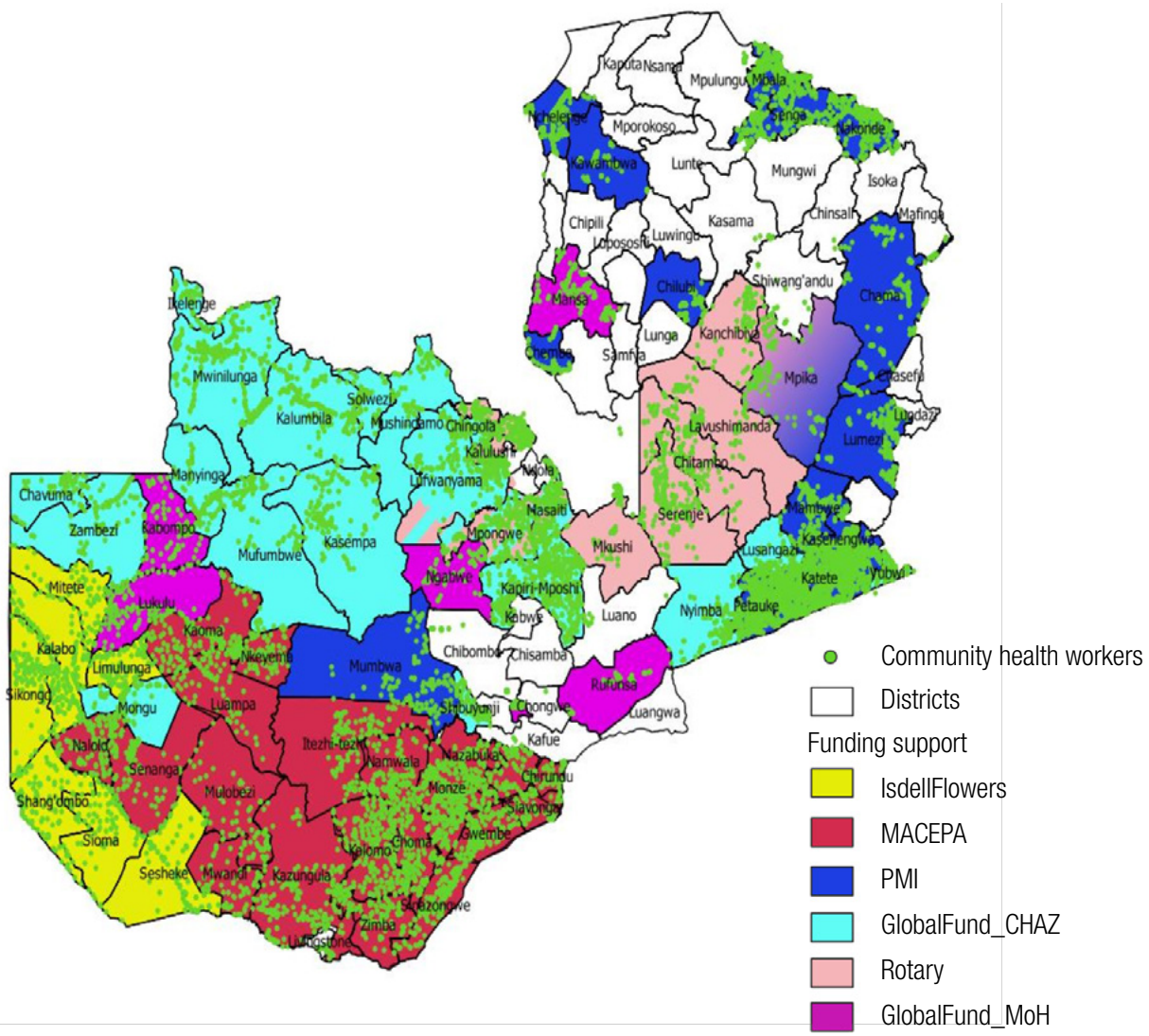
Zambia implemented RAS as part of its iCCM strategy in 2017, after a successful pilot in 45 communities in the Serenje district[14]. In the scale-up phase, RAS was deployed by over 6,000 CHWs in over 45 districts in 1,272 communities with poor access to health care. Key success factors included: (a) the training of 16,500 CHWs in malaria management since 2017; (b) community mobilization that increased program ownership and RAS uptake and facilitated referrals with or without emergency transport services; (c) training of CHWs on following up severe malaria cases after recovery; and (d) the presence of qualified staff at the health facilities so that post-referral treatment with Inj AS and ACTs was assured.

The implementation of RAS in this setting resulted in a reduction of the CFR of 97% and 87% in the pilot and scale-up districts, respectively, with an estimated 496 lives saved. Challenges included a lack of emergency transport services in some communities and stock outs of RDTs and ACT at the CHW level. Providing CHWs with a means of transport (e.g., bicycle) would help them to follow-up on RAS recipients. Zambia's experience shows that strengthening the health system, including iCCM, is paramount to successful RAS implementation. CHWs have great potential to reduce malaria morbidity and mortality provided they are trained in case management, supported by regular supervision, and supplied with commodities. Their work is enhanced when they can provide care within a supportive system with community social mobilization and functioning emergency transport. Additionally, training staff at lower-level health facilities to provide subsequent treatment with Inj AS is of vital importance[15].

14. Green, Cathy, Quigley, Paula, Kureya, Tendayi, Barber, Caroline, Chizema, Elizabeth. et al. (' 2019)' . Use of rectal artesunate for severe malaria at the community level, Zambia. Bulletin of the World Health Organization, 97 (' 12)' , 810-817. http://dx.doi.org/10.2471/BLT.19.231506
15. https://www.transaid.org/wp-content/uploads/2022/02/FINAL-MAM@Scale_EvidenceBrief_Final-Results-24.01.22.pdf

Figure 4: CHW rollout map by district by partner as of 20th October 2021

Source/date: NMEC MRR, last updated October 20th, 2021



MMV's survey of the severe malaria patient journey

MMV carried out a survey among 396 health workers (CHWs, pharmacists, nurses and physicians) involved in the management of severe malaria and analysed aggregated information from 1,228 patient registries in 2020 in five countries (Ghana, Uganda, Burkina Faso, Nigeria and DRC). Results showed that the CFR in severe malaria during hospitalization ranges from 6% in Nigeria to 15% in Burkina Faso and Ghana, and is approximately 20% in DRC and Uganda. In most cases, delay in referring the patients was seen as the leading cause of mortality. At onset of symptoms, 63% (Uganda) to 95% (DRC) of patients self-medicated. Duration between onset of malaria symptoms and consultation depends on where patients go for consultation and varied from 2.1 days (Uganda) to 4.5 days (Nigeria) when patients consult CHWs and 3.3 days (Uganda) to 4 days (Nigeria) when patients are admitted to hospital.

At hospital level, the majority of patients received Inj AS (60–80% in Nigeria and DRC, over 95% in Burkina Faso, Ghana and Uganda). Injectable treatment is given for 1 (Ghana and Uganda) to 2 days (Burkina Faso, DRC, Nigeria). At least 90% of severe malaria patients received an oral treatment after IV treatment. Oral ACT was given to all patients in Ghana and Uganda, 90–95% of patients in Burkina Faso and DRC, and 75% of patients in Nigeria. Half of patients received their first oral ACT at hospital level in DRC, Nigeria and Uganda, 20% in Burkina Faso and 85% in Ghana.
The findings presented in this session differed significantly to those found by CARAMAL and reflect important differences between countries and settings. Both represent real-life situations and point to a fluid reality around RAS implementation. It should be noted that there were differences in both the methodology and the sample size between the CARAMAL project and the market research that do not permit direct comparison of the findings. Continuous monitoring and evaluation will be of crucial importance to ensure that RAS achieves its full potential in reducing malaria mortality.

Peter Olumese, WHO: WHO's severe malaria guidance

WHO updated the new malaria guidelines in February 2021. In these guidelines, WHO recommends where Inj AS is not available, children under 6 years of age should be treated with a single rectal dose (10 g/kg body weight) of artesunate and referred immediately to an appropriate facility in which parenteral treatment is possible. Rectal administration of a single dose of artesunate as pre-referral intervention reduces the risk of death and neurological disability, as long as this initial treatment is followed by appropriate parenteral antimalarial treatment in a health facility. Initial rectal or parenteral treatment must always be followed by a full 3-day course of ACT. The WHO recognizes RAS as a lifesaving intervention in these children and WHO's recent information note on the use of RAS following publication of the results of CARAMAL must be seen in this context and does not override current WHO guidelines[16].

16. https://apps.who.int/iris/rest/bitstreams/1415604/retrieve

WHO announced that it will continue to support and facilitate countries in strengthening their health systems to maximize the safe and effective deployment of RAS and other pre-referral medications at the community level as part of the continuum of care for severely sick children.

WHO made several important recommendations, listed below:

WHO recommends:

- RAS as a lifesaving intervention should be made available to all children in accordance with WHO guidelines recommendations;
- Strengthening of referral and post-referral services should be prioritised and supported on a continuing basis;
- RAS must not be withheld from any child with severe febrile illness where intramuscular artesunate is not available.

WHO urges:

- Malaria-endemic countries to continue with implementation and scale-up of malaria case management services as per their national treatment policies and guidelines;
- All stakeholders to ensure quality of care in line with existing WHO recommendations at all levels of the health care system considering the full cascade of care from the community to the hospital levels;
- Countries and partners to continue support the rational use of antimalarial drugs to mitigate the selection and spread of artemisinin resistance;
- Funders to support not only medicines and life-saving commodities, but also the systems required to safely and effectively deploy these interventions at the community level as part of a high-quality continuum of care;
- Procurement agencies and manufacturers to ensure continued supply of RAS.

WHO also clarified that it will not issue criteria or indicators to monitor when health systems are ready to deploy RAS. Rather, WHO's guidance is that RAS should be deployed responsibly, and that, as part of RAS implementation, strengthening referral systems and quality of care at hospital level should continue, ensuring access to correct management of severe malaria. Actions to be taken to achieve this will be different for each country and setting.

Comments by Hans Rietveld, Medicines for Malaria Venture: implications for procurement

Volumes of procured RAS have been low and the annual worldwide need can be produced in a single production run. However, the shelf life of RAS is limited, and this presents the WHO-prequalified RAS manufacturers with a need for accurate visibility of country demands for 2022 and beyond. A recent CHAI forecast exercise showed that needs are expected to stay relatively stable in the coming years (2.5 million capsules of RAS in 2022; 2.6 million RAS in 2023 and 3.0 million RAS in 2024), but this will depend on donor commitments, country prioritization and importantly, WHO guidance.

Comments by Jordan Burns, the US President's Malaria Initiative (PMI)

PMI and its implementing partners are committed to working with country programs to support several facets of severe malaria management, from procurement of RAS and Inj AS to the training and supportive supervision of health workers. In PMI's new strategy (2021–2026) there is an emphasis on strengthening community health services including primary healthcare. To address the many complexities and bottlenecks in the referral chain, PMI will work with countries to improve quality of care at both community and facility levels. Supply chain strengthening remains a priority, including quantification, supply chain visibility and use. In 2021, PMI procured 1.1 million RAS capsules for 18 countries and 14 million vials of Inj AS for 22 countries. The RAS supply chain is particularly challenging due to the limited number of suppliers, countries requesting relatively small quantities and manufacturers having minimum order quantities and limited production runs. PMI will work with country programs and other stakeholders to implement RAS in line with WHO recommendations and will at the same time work to avoid interruptions in services and the supply chain.

Comments by Estrella Lasry, GFATM

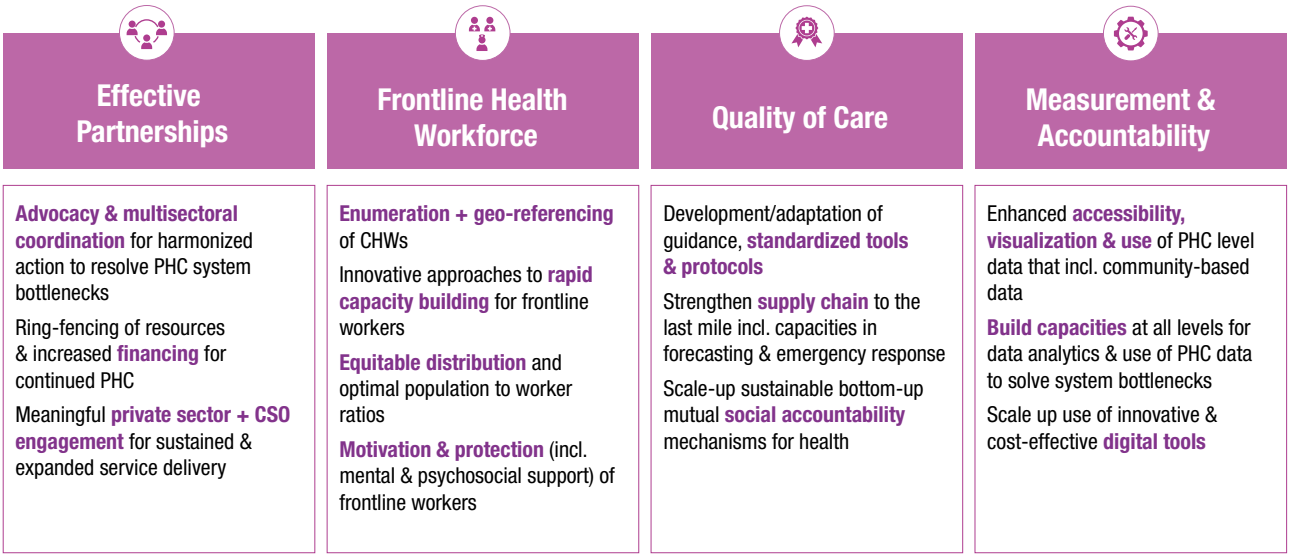
GFATM has supplied RAS to countries for several years. It temporarily halted procurement of RAS after WHO's MPAG minutes were published, while awaiting further WHO guidance, but has now reversed this decision and will discuss with each individual country how to move forward. GFATM sees the results of CARAMAL as a call to action and an opportunity to work on health system strengthening in order to make an impact on severe malaria and overall population health. GFTAM will continue to work with countries and partners to strengthen community health networks and structures to enable the optimal use of RAS and give broader health system support to improve the continuum of care. It will work with countries, malaria and non-malaria partners to collect evidence on current gaps and to find solutions that are people-centred and tailored to the needs. This is taking place in the current funding cycle while collecting evidence to inform the next funding cycle. GFATM has been working with the University of Geneva and other partners in applying AccessMod — a WHO tool — in multiple countries looking at geographical access to services across diseases (e.g., testing, treatment and referral services for simple and severe malaria case management) at community level and health facilities (public and private sector), in close collaboration with national governments. These studies look at access from the perspective of realistic travel time (by foot and different vehicles for rainy and dry seasons), shed light on service geographic accessibility given disease burden, and inform optimal placement of CHWs and improvement of service referral networks.

Maureen Momanyi, UNICEF: the importance of community health systems in severe malaria

Community systems are integral for scaling up access to severe malaria case management as part of primary health care, especially among marginalized and hard to reach communities. To effectively deliver a multi-sectoral package of interventions at community level inclusive of malaria care (screening, case management and referral), a robust system is required that comprises the 'formal' health system architecture (e.g., CHWs, outreach posts) embedded within the broader health system and effectively linked with 'informal' community-based service delivery platforms. At the Institutionalizing Community Health Conference (ICHC) 2.0 in 2021, countries reflected on progress made in strengthening and institutionalizing community health within broader national health systems. To address challenges impeding progress, both state and non-state actors collectively agreed to invest in a set of priority actions, broadly classified in Figure 5 with a further emphasis on the need to:

- Professionalize and motivate community health workers (CHWs) — in line with WHO's 2018 guidelines that call for CHWs to receive a financial package that corresponds to their job demands, complexity, number of hours worked, training and roles they undertake. In addition, to go beyond this to explore and contextualize nonfinancial incentives such as supervision, capacity building, career pathway, equipping and protection (mental health and psychosocial support). Where CHWs are common and well supported, RAS implementation has led to optimal outcomes (Zambia, Malawi) whereas in countries where CHWs are sparse or poorly motivated the opposite was seen (DRC, Nigeria).
- Increase sustainable and equitable domestic/external financing for community health as part of PHC informed by national strategies and integrated costed plans and budgets. Prioritize increasing domestic fiscal space whilst working to improve efficiencies — making smarter investments in a limited fiscal space, with prioritization of zero-dose communities whilst simultaneously working to reduce fragmentation and verticalization of PHC funding streams and aim for better coordination across funders and allocation that is aligned to country priorities.
- Improve the quality of service provision at community level, including strengthening referral and counter-referral mechanisms, that builds on clinical and non-clinical performance monitoring to include meaningful engagement of communities and scalable approaches to social accountability.

Figure 5: Next steps: consolidating community health within PHC for health systems resilience



Ensure country progress in institutionalizing community health as a core component of multi-sectoral PHC at community level is tracked, through the use of data analytics and digital technology to enhance the access to and use of community level health data.

Reflections from Malawi

There were 9,000 CHWs active in Malawi in 2021. They constitute over half the health workforce. Malawi continues to invest in iCCM and has a National Community Health Strategy (2017–2022) which outlines a new community health system in which community health cadres, both formal and non-formal, deliver services of the Essential Health Package, with a focus on child and maternal health.

Severe malaria management relies on community engagement and clinical management (diagnosis, prompt pre-referral intervention with RAS, community referral and follow-up of treatment adherence afterward). Many lessons were learnt and successes achieved in reaching remote communities and providing reliable stocks of malaria drugs and trained human resources at community level.

Among challenges that were encountered was a lack of refresher training among iCCM workers which led them to fail in recognizing danger signs of severe malaria. Another challenge was the unreliable organization of transport for referrals in communities.

For additional reading: A cohort study in Malawi assessed the role that targeted Information Education and Communication tools play in health seeking and the delivery of care. One of the findings was that these tools for the CHWs alongside a referral slip protocol that formally links the levels of care enhanced the continuum of care[17].

17. https://www.severemalaria.org/rectal-artesunate-information-education-and-communication-report-rasiec

Pascal Ringwald, WHO: update on artemisinin resistance in Africa

Validated markers of three K13 artemisinin-resistant mutant parasite strains have been found in Rwanda, Uganda and Horn of Africa. All mutant strains had a multifocal African origin. It is not yet explained what the main drivers for this emerging resistance to artemisinin are. There is a risk that using oral and parenteral artemisinin-based monotherapies, incomplete or substandard ACT treatment can cause the selection of mutant resistant strains. Although all ACTs are still highly effective on the African continent, this highlights the pressing need to follow-up artesunate/artemether injection and RAS with full ACT treatment. WHO is developing a strategy to delay artemisinin resistance in Africa together with partners. This will include three steps: a compilation of all information on resistant strains in Africa, identification of the key determinants and effective interventions and the development and implementation of the containment strategy.

Hans Rietveld, MMV: update on RAS stability and shelf life

In the WHO Public Assessment Report (WHOPAR), the WHO Prequalification Programme provided recommendations on the storage of rectal artesunate 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 at most 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 month****s depending on the remaining shelf life of a given batch and severity of the ambient conditions where the batch is to be distributed.'*

This guidance regarding short-term stocks for CHWs was challenging to implement, as distribution of RAS to CHWs is not regular and sometimes RAS capsules had to be destroyed as a consequence.

In the context of CARAMAL a real-world study on the stability of RAS was carried out in an area of Nigeria where the ambient temperature is almost continuously above 30°C. Samples of RAS kept by CHWs were taken at 6, 9 and 12 months. The results of the analysis showed that RAS passed tests even 6 months after delivery to the CHW. This led to updated WHO guidance[18].

18. https://extranet.who.int/pqweb/sites/default/files/MA123part1v1_0.pdf https://extranet.who.int/pqweb/sites/default/files/MA124part1v2_0.pdf

> "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 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."

Studies into the stability of RAS are continuing.

Concluding remarks

The introduction of RAS in countries with functioning health and iCCM systems has been shown to make an important impact on mortality and morbidity of severe malaria in real-life circumstances. In deprived and remote areas such as those observed by the CARAMAL project, RAS is unlikely to make a significant impact without further health system strengthening. The CARAMAL study results highlight that mortality gains will largely depend on improving the performance of health systems rather than exclusively focusing on the introduction of a new drug. Improved management of severe malaria requires a 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 good treatment practices at the referral facilities, to discharge planning and follow-up. Other factors which were shown to affect RAS uptake and its correct use as a pre-referral intervention are community perception, treatment seeking behaviour, acceptability, SBCC, the presence of transport modalities to referral centres and involvement of the private sector and traditional healers.

The meeting was concluded with a pledge of support and a clear encouragement by all relevant organizations (among others WHO, UNICEF, PMI, GAFTM, MMV, CHAI) for countries to implement RAS according to WHO guidelines. However, crucially, without investments to address the broader health system challenges, RAS cannot achieve its potential and help reduce child mortality. Countries were asked to compile evidence on the existing gaps in the continuum of care for severe malaria in each setting, and propose and pilot tailor-made and innovative solutions to address these.

Photos: Toby Madden (pp 2, 4 & 9), Elizabeth Poll/MMV (Cover & p 22), Damien Schumann (pp 14 & 16)
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Annexes

Annex 1

Agenda

Day 1 – Global updates, research and experiences with severe malaria care 1 – 4pm GVA			
Presenting time (approx.)	**Topic**	**Content**	**Speaker**
5 min	Welcome Opening		MMV Co-chairs: Elizabeth Chizema Olugbenga Mokuolu
15 mins	Progress update toward adoption of RAS and Inj AS	Landscaping update and highlights of Severe Malaria	CHAI
45 mins	Experiences improving severe malaria care along the continuum Part 1	Opening • CARAMAL: intro to continuum of care and overview of learnings (15 min) Series of 10 min presentations: • Patient Journey Market Research • Uganda • Sierra Leone	Moderator: Elizabeth Chizema Christian Burri MMV Maureen Amutuhaire Anitta Kamara
10 mins	Break		
40 mins	Experiences improving severe malaria care along the continuum Part 2	• Senegal • DRC • Nigeria • Zambia	Seynabou Gaye Faye Alain Mugoto Koki Abdullahi Stephen Bwalya
40 mins	Panel Discussion with Q&A	Panel on managing febrile children across the continuum of care	Moderator : Olugbenga Mokuolu CARAMAL countries [Antoinette Tshefu, Liz Omoluabi, Phyllis Awor] and other presenting countries to further discuss experiences/implications
10 min	Recap and close Day 1		Co-chairs

Day 2 – Implications for policy, implementation, procurement and supply chain 1 – 4pm GVA			
Presenting time (approx.)	**Topic**	**Content**	**Speaker**
10 min	Recap from Day 1	Rapporteur	Margriet den Boer
15 min	Artemisinin resistance Q&A	Latest evidence and implications for RAS and Inj AS	Moderator: Olugbenga Mokuolu Pascal Ringwald
15 min	WHO severe malaria guidance		Moderator: Olugbenga Mokuolu Peter Olumese
20 min	Implications for procurement and supply chain	Statements from key agents	Moderator: Olugbenga Mokuolu PMI TGF MMV
20 mins	Strengthening Primary Health Care including Community Health		Moderator: Elizabeth Chizema Maureen Momanyi, Unicef New York, in collaboration with WHO Child Health
40 min	Break-out session	Formulate further questions for WHO, TGF, PMI, UNICEF and CARAMAL team	4 clusters of countries
10 min	Break		
40 min	Panel discussion	Responds to questions from countries	Moderator: Elizabeth Chizema PMI, TGF, WHO, Unicef and CARAMAL team members (same as above)
10 min	Wrap up and conclusions		Co-chairs

Annex 2

Questions and Answers Day 1:

Participant: Ombeni Mwerinde **To Presenter:** Theodoor	**Question:** Are there estimates for the need for both Inj AS and RAS? Which is useful to understand the gap between the procurement volumes and the need?

Answer 1:
Eliza: Hi Ombeni, estimates of need and demand for severe malaria commodities will be published as part of our long-term forecast publication for the forecasting project in June of this year.

Participant: Andrea Bosman **To Presenter:** Christian Burri	**Question:** Treatment seeking behaviour as shown in slide 3 is very complex: was there any study of treatment seeking behaviour to evaluate changes, if any, before and after the RAS deployment? Which interventions, particularly BCC was implemented to support RAS deployment? With only 1% children receiving full treatment (Inj AS + ACT) at referral facility in Nigeria, is it surprising that that CFR was even higher after the deployment of RAS at CHW and PHC levels? Why there were very low number of children receiving RAS in Nigeria, both at CHW and PHC levels? It will be good to know what was done to prepare the roll-out of RAS in these three countries, assuming it was a new deployment coordinated by the project teams of CHAI and UNICEF. What is still unexplained what was done in the CARAMAL project to ensure good deployment of RAS in very complex environments, in order to ensure the effectiveness of the intervention.

Answer 1:
Phyllis Awor: In Uganda, RAS was distributed from centre to the rural facilities through routine processes. CHWs then were expected to collect their drugs from the nearest health centre. There were many challenges with this approach. So CARAMAL/CHAI supported the CHW supervisors with transport to re supply CHWs
Christian Burri: What is still unexplained what was done in the CARAMAL project to ensure good deployment of RAS in very complex environments, in order to ensure the effectiveness of the intervention - Unicef through its country offices made significant efforts to ensure training of all relevant health staff, population information and provision of commodities - the example of RAS is in my modest view also an example of the complexity of the introduction of any intervention in areas as deprived and remote ascertain DRC /Nigeria. Access not only to health, but to the population and service providers remain huge challenges - reflected in the persisting cases of death e.g., in malaria over the past couple of years.

Answer 2:
Burri: With only 1% children receiving full treatment (Inj AS + ACT) at referral facility in Nigeria, is it surprising that that CFR was even higher after the deployment of RAS at CHW and PHC levels? Why there were very low number of children receiving RAS in Nigeria, both at CHW and PHC levels? ACT treatment was low in Nigeria in both study phases - before and after the introduction of RAS. RAS use was low because of programmatic and supply issues. So we expected actually no difference in CFR between the two time period. The reasons for a steep increase in CFR in the second phase is probably linked to other climatic and health system factors. This also corresponds to the peak of the Corona outbreak.

Answer 3:
Sources shared: A paper on post-referral treatment: Signorell et al. https://doi.org/10.1101/2021.11.26.21266917
There is a very detailed analysis on care seeking in Uganda (Brunner et al. https://doi.org/10.1101/2021.12.09.21267055)

Participant: Estrelle Lasry **To Presenter:** Burri	**Question:** Thanks, Christian, for the important presentation. Clarification question, which RDTs were used to assess D28 positivity?

Answer:
Theodoor: Initially a HRP II Pf RDT, later on a Pf/Pan, from WHO PQ'ed suppliers

Participant:	Question:
Wilson Were **To Presenter:** Burri	Christian, from the data it was clear that there were differences in where RAS was used, In Uganda where you have good impact, it was used at the community level while in DRC at PHC facilities. In addition, there was more mismanagement of the cases at the referral facilities particularly in Nigeria, how then do infer that the problem is RAS. Secondly, this was an observational study, how did you control for differences between the countries?

Answer:
See responses to questions to Andrea Bosman and Peter Olumese

Participant:	Question:
Peter Olumese **To Presenter:** Burri	The comparison was pre vs post intervention. Do we know what happened to those who did not receive RAS during the implementation phase. What was the CFR at that them in that group. A lot more information is needed on the study methodology to properly interpret the results with regards to CFR @Christian, the important contexture factors in the pre and post intervention phases are unfortunately not highlighted in the preprint or presentations. So the presentation gives the impression that all other co-founders were controlled for.

Answer 1:
A lot more information is needed on the study methodology to properly interpret the results with regards to CFR: There are currently 11 publications on preprint servers or submitted; we tried to analyse those data in very detail and to consider the confounders and to adjust for biases - not possible to summarize on one slide, sorry

Answer 2:
I think there should be no comparison between the Gomes studies with this. Gomes et al was a head-to-head comparison. This study used a pre-intervention survey as control and strictly observational - in my view, the comparison has to be done, since the Gomes study was the trigger for the recommendation of RAS, and because this is an example (of many) that of many that results from (necessary) clinical trials cannot be 1:1 translated into real live without implementation research and the necessary adjustments (following the words of Dr. Soumya Swaminathan, Chief Scientist of WHO

Answer 3:
Burri: The CARAMAL study was an observational study, and yet the evidence on which RAS was introduced was based on RCTs. While the challenges highlighted by CARAMAL are very relevant in improving quality of care and clinical outcomes, they are not unique to RAS. Why stop the intervention which is based on RCT, so the question is, Do we have enough evidence to stop this life saving intervention? - it is very clear that the challenges is not restricted to RAS and I tried to underpin this in my presentation. RAS per is not a "bad" intervention and this is what the WHO information letter states - it just has to be reflected very carefully where and how RAS is implemented to prevent this "lifesaving" intervention turns into the opposite. RCTs are the basis of development of interventions, but not good enough for implementation of tools in very complex environments, for this effectiveness and real-world data studies are important.

Answer 4:
Prompt immediate antimalarial treatment of children with severe febrile disease in malaria endemic area saves lives. The GMP statement implies that RAS as a treatment option at the community level should be considered with utmost caution or even halted. What treatment options that have shown to be more feasible to implement? - First of all we have to be cautious: RAS is no "treatment option" and this understanding has to be clear - it is a "pre-referral intervention" and has to be followed up by proper treatment with Inj AS and ACTs. The treatment option at CHW/PHC level are ACTs if there is no suspicion / ICCM danger signs of severe malaria.

Answer 5:
Christian, from the data it was clear that there were differences in where RAS was used, In Uganda where you have good impact, it was used at the community level while in DRC at PHC facilities. In addition, there was more mismanagement of the cases at the referral facilities particularly in Nigeria, how then do infer that the problem is RAS. Secondly, this was an observational study, how did you control for differences between the countries? - There is no control for differences between the countries - observational. Fact is that the Health Systems in the three countries are set up in very different ways - CHW (VHT in Uganda) are very frequent in Uganda, but very few e.g., in the DRC; distances / travel time to the next competent HF in Uganda was generally <15', whereas in the DRC / Nigeria is was very often several hours. These differences and shortcomings are all not directly related to RAS, but to how RAS can be used - and this is reflected in the WHO guiding letter

Answer 6:
Your point that we should have included all possible confounder to make a better before-after comparison is of course well taken. The problem is that there are so many such factors, and many cannot be measured easily, that it is very difficult in practice. We attempted to control for many confounding factors, but certainly failed for a lot of others. On the other hand, the fact that RAS does not seem to make an impact makes the interpretation a little easier. In the DRC and Nigeria it is sure that RAS did not improve CFR, and in Uganda there was an effect but the absolute difference was small.

Participant: Bhargavi Rao **To Presenter:** Burri	**Question:** Any insight into why such low treatment (injectable AS/ACT) completion in Nigeria? Were other treatments used? This has to be more than stockouts.

Answer:
Prudence: Bhargavi MC did an audit of the provision of care in hospitals in Kana Kaduna Katsina and Jigawa. The main problems found was lack of knowledge of staff of the actual treatment guidelines, lack of diagnostic services shortage and high turnover of staff, lack of supervision and quality care monitoring, over work of staff, stock outs etc. Quality improvement committees were set up and there was some improvement but especially the follow up of Inj AS with ACT and discharge follow-up

Participant: Jocelyn Razafindrakoto **To Presenter:** Burri	**Question:** Why these negative output (no impact on mortality, low compliance with WHO guidance) not suspected during the preliminary study?

Answer:
Why these negative output (no impact on mortality, low compliance with WHO guidance) not suspected during the preliminary study: Not sure what preliminary study you are referring to - Gomes et al. was a clinical trial, so had many factors we found to be critical controlled (monetary concerns, repeat treatments leading to biased decisions, stockouts, transport for referral etc.)

Participant: Bruno Moonen **To Presenter:** Burri	**Question:** How do the finding align (or not) with the recent publication by Amboko et al.?

Answer:
How do the finding align (or not) with the recent publication by Amok et al. ? - sorry, Bruno, would have to look much closer into the Amboko study. What is certainly clear, is that the areas of DRC and Nigeria where we worked are of high interest and special, since they are very representative for those areas where health systems are most deprived, and suboptimal decisions are made because of the lack of any means, and because every family has to make numerous decisions over a year (assuming 5 kids, 5 malaria episodes each kids, 5 other episodes each kid = one decisive decision per week per family !!! With this perception, trust and $ become even much more of importance.

Participant: Cathy Green **To Presenter:** Burri	**Question:** Is there any evidence to suggest that the CHVs ran out of supplies intermittently? I think they were given a very small number of capsules at any one time. That might have a bearing on whether they were able to offer the full dose - stock-outs were part of the issue:

Answer:
Is there any evidence to suggest that the CHVs ran out of supplies intermittently? I think they were given a very small number of capsules at any one time. That might have a bearing on whether they In general, CHW /PHC received 2 capsules at a time, as usage was unsteady this inevitably leads to interruption of stock in case of high patients frequencies; there were also other factors, like “saving the RAS for potentially more severe cases”

Participant: Elizabeth Omoluabi **To Presenter:** Céline Aubert	**Question:** Patient journey market: as no primary caregiver was interviewed, are you not concerned about social desirability bias, where the health care providers report that they did the right thing, made the prescription but there is no confirmation from the patient or caregiver. The CARAMAL study collected data from primary caregivers as well as health care providers. This could explain some major differences in results with the market research

Answer:
This is a good point about the absence of caregiver in our survey. It will be interesting to collect their views as well. Given our budget constraints, we had to make a choice and decided to focus on the health care professionals to map the continuum of care.

Participant: Eric Tchinda **To Presenter:** Dr Denis	**Question:** What are the provisions that are in place in your country to ensure the continuum of care, when we know that sometimes the health facilities are very far from the populations and the means of transport to get there are not always available?
Answer: Theodoor: CARAMAL did not implement specific interventions around referral. It was meant to introduce RAS in real life settings with minimal supportive interventions	
Participant: Andreas Bosman **To Presenter:** Dr Denis	**Question:** From the presentation of Dr Rubahika seems that community acceptability is an issue in rural areas of Uganda and this calls for specific BCC interventions to address this, as part of RAS deployment
Answer: NA	
Participant: Yacouba Savadogo **To Presenter:** All	**Question:** Thanks to all. Very good presentations. The problem in some regions of the Sahel, the insecurity makes that the health centres and district hospitals are closed, no possibility to refer a patient because the ambulances are withdrawn, and there is only the iCCM as a possibility to save lives. What do we do in these situations? Do nothing or do the RAS and supplement with ACT in the community?
Answer: To be discussed on day 2	
Participant: Hacque Twaibu **To Presenter:** Anitta Kamara	**Question:** On the death has the country Sierra Leone did something on health seeking behaviour? This may contribute to more dying on the way.
Participant: Purdence Hamade	**Comment:** Timely uptake of referral is another big issue as well which need strong community engagement
Participant: Tewuh Fomunyam **To Presenter:** Anitta Kamara	**Question:** The referral channel seems long when we consider the classic signs of severe malaria and how fast action needs to be taken. Is there any evidence that the referral channel as exists causes delays in proper treatment onset in Senegal?
Answer: Seynabou Gaye: the delays noted in the references in Senegal often result from lack of financial means and rolling logistics	
Participant: Jeanne D'arc Ntiranyibagira	**Comment:** It's Jeanne from Djibouti. It could be better to have an idea on deaths due to malaria among under five years age without using RAS.
Participant: Tewuh Fomunyam	**Question:** What are some of the strategies to countries have adopted to improve relay with ACTs after injections in the treatment of severe malaria? At 4.4%, that is alarming.
Participant: Joe Mugasa	**Comment:** RAS seems to make impact in areas where health system is strong and referral systems are well defined.
Participant: Tewuh Fomunyam	**Comment:** An RDT takes 15mins to execute and read. Testing before initiation of treatment should not constitute a delay as diagnosis needs to be confirmed. On the other hand, if it is retesting a patient who has been previously diagnosed and referred, then I agree it could be viewed as constituting a delay

Participant: Wilson Were	**Comment:** I think we are putting too much emphasis on RAS, RAS as a drug is effective but one prereferral dose cannot be expected to address all the system challenges that colleagues have outlined above. It is the same thing we are seeing at facility level with providing appropriate treatment. Are we going to stop health workers from giving IV artesunate just because they don't complete treatment as recommended? I think the CARAMAL study has highlighted the issues that need to be addressed and should be the focus, not the drug.
Participant: Blaise Kouadio To all	**Question:** How does case management at community level contribute to reduce significantly severe malaria at facility level? Do you have evidence (Data or trend) from your countries?
Participant: Caroline Barber	**Comment:** My sincere thanks to all the presenters today for the excellent presentations. Really educational. There is more about the Zambia approach and results in this brief - https://www.transaid.org/wp-content/uploads/2022/02/FINAL-MAM@Scale_EvidenceBrief_Final-Results-24.01.22.pd

Questions and Answers Day 2:

Participant: Andrea Bosman **To Presenter:** Pascal Ringwald	**Question:** Are there other studies which have shown an increase in K13 artemisinin validated markers appearing after a single dose of artesunate given either by rectal or parenteral administration, and not present prior to administration? please can you share the details?
Participant: Andrea Bosman **To Presenter:** Pascal Ringwald	**Question:** Pascal can you explain the meaning of class I-IV in your slide as it was not discussed yesterday?

Answer:
Class 1: baseline- before RAS roll out
Class 2: is representing the samples collected within endline part of the project from participant prior any treatment and categorized as severe malaria.
Class 3: is representing the samples collected within endline part of the project from participant who received RAS and that were referred to local health facilities. The sample collection was performed concomitantly to RAS administration. Regarding epidemiology of resistance, these samples are similar to group 2 samples (ie representative of mutant circulation in population).
Class 4: is representing the samples collected within endline part of the project from participant who received RAS but who do not complete the referral at health facility and thus do not receive ACT treatment. These samples were collected 28 days after RAS administration

Participant: Denis Rubahaki **To Presenter:** Pascal Ringwald	**Question:** Pascal what do you mean by combination of IV artesunate and iv quinine in places with suspected artemisinin resistance (also raised by Denis in breakout)
Participant: Bruno Moonen **To Presenter:** Pascal Ringwald	**Questions:** Are there any hypothesis on what the main drivers of the emergence of resistance could be specifically for Rwanda and Uganda? Are these different from GMS?

Answer:
No we don't have any hypotheses

Participant: Karen Barnes **To Presenter:** CARAMAL	**Question:** Is there any evidence from the qualitative component of the CARAMAL study that partial response to RAS deterred adherence to referral?

Answer:
in all three CARAMAL countries the referral rates were slightly lower (by about 10%) in RAS recipients compared to non-RAS recipients. But there is not much qualitative information to explain that difference.

Participant: Paula Quigley **To Presenter:** CARAMAL	**Question:** Since the initial guidance for RAS implementation was in combination with appropriate referral, it seems strange to set up a study that doesn't include this as an integral part of the study. Almost bound to fail! What was the rationale behind this?

Answer:
making referral part of the RAS implementation is of course a good suggestion. But at present there are no such referral support systems almost everywhere in endemic countries. Hence the decision was taken to test RAS in the circumstances most resembling "real world" at this point. But we certainly support the notion that referral conditions should be strongly improved.

Participant: Pascal Ringwald **To Presenter:** Peter Olumese	**Question:** Based on how many studies was RAS introduced in the treatment guidelines?
Participant: Denis Brown To All	**Question:** At present, the Global Fund has stopped all orders of rectal artesunate. Manufacturers can only keep their production lines working if they receive orders and do not have to destroy their existing stocks that reach expiry of shelf-life.
Participant: Christian Nsanzabana **To Presenter:** Peter Olumese	**Question:** So should countries stop implementing RAS, and wait to get more evidence, or continue the implementation?

Answer 1:
Countries should not stop implementing RAS, we will continue to support countries as they continue to implement and scale up RAS. We have no new evidence, WHO is working with countries to help them continually strengthen the delivery platform for RAS

Answer 2:
Christian N: thanks for your response. This is quite different from the information note published on 27 January, it clearly states: Countries that have not yet introduced pre-referral RAS but are considering doing so should withhold implementation. Could you please clarify? Thanks.

Answer 3:
Countries presented yesterday of innovative ways of improving referrals systems, so we cannot make a blanket statement. Even where RAS studies were undertaking, things may have changed today in terms of strengthening the system. While these are country-driven we should continue to share best practices where things are working

Answer 4:
Peter: I agree with you that "more focus has to be put on the most deprived and isolated areas where many of the fatalities are still occurring". Just that it should not be withholding RAS from them, because that further increases the chances of fatalities from severe malaria. The focus should be on how to rapidly develop locally acceptable mechanism to ensure that they get to benefit from services from the nearest healthcare facility including the ability to get to them after pre-referral treatment and guaranteed effective post referral treatment

Participant: Jocelyn Razafindrakoto **To Presenter:** Peter Olumese	**Question:** Do you think that the WHO guidance reflects the conclusion of this presentation? The guidance is more focused on RAS, while the conclusion of this presentation is about system and continuous of care. What is easier, stopping country effort on RAS or reinforcing country capacity to ensure ACT treatment at Health facility?
Participant: Karen Barnes	**Comment:** The Global Fund stopping its RAS orders may make it difficult for countries to not stop its use, which is at tension with current WHO recommendation.
Participant: Theodoor Visser **To Presenter:** Estrella Lasry	**Question:** Can Global Fund provide an example (real or hypothetical) where and why planned RAS orders have been halted?
Participant: Denis Broun To all	**Question:** Two questions for the sagacity of participants: • has there been a precise mapping of malaria deaths of children below 6 years? It would be useful to see if these deaths occur within easy or difficult reach of a referral facility. • As a manufacturer of rectal artesunate, Strides would be ready to supply the pack of 2 rectal caps of 100mg together with dispersible artemether/lumefantrine (20/120) to make sure that RAS emergency treatment is followed by adequate 3-day oral treatment in the community, if referral cannot happen.

Answer 1:
Estrella: GF is working with University of Geneva and WHO on the development of accessibility studies of multiple countries looking at access to care including community, primary healthcare facility and secondary facility (public and private sector). These studies look at access from the perspective of distance (by foot and different vehicles), as well as at socioeconomic determinants of access. To my knowledge there are only individual country maps and not a general map of access

Answer 2:
Lengeler: there is no systematic assessment of deaths in children, including their location, anywhere on a large scale (to the best of our knowledge). CARAMAL findings suggest that quality of care, especially in referral health facilities, is a bigger determinant than distance per se.

Participant: Harriet Napier **To Presenter:** Peter Olumese	**Question:** To clarify, the question is not about new or updated guidance, but about metrics along this cascade of care that can help a country determine whether or not we can safely scale RAS. How do we determine if we should or should not proceed?

Answer:
There is no such metrics, and no plan I know of to develop that. RAS is only one of the interventions delivered through the system, so it is not likely that we can develop a metrics just for RAS. Health systems are continuously being improved and being responsive to the prevailing situations… So the question is not RAS but how to continuously improve the system that delivers RAS and other pre-referral medicines

Participant: Harriet Napier To All	**Question:** How are countries communicating these findings (in particular the risks associated with RAS and Inj AS) to caregivers/ healthcare workers/health program managers?

Annex 3

Day 1 Attendee list:

Family Name	First Name	Affiliation	Country
Abdu	Halima	UNICEF	LIBERIA
Abdullatif	Hadjira	Programme nationale de lutte contre le paludisme	COMOROS
Acuna	Gonzalo	MMV	SWITZERLAND
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Agbozognigbe	T. Didier	Ministère de la santé	BENIN
Ahouansou	Charlemagne	MS / DDS Collines	BENIN
Akuffo	Miriam	CHAI	GHANA
Alpha	Raymond	Population Services International	SIERRA LEONE
Amadou	Hamadou	Chemonics Inc	CAMEROUN
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Amutuhaire	Maureen	Ministry of Health	UGANDA
Andriamanjato	Hery	JHPIEGO	MADAGASCAR
Angale	Ibrahim	Clinton Health Access Initiative	NIGERIA
Asiam	David-Living	INTEPRETER	GHANA
Atcha-Oubou	Tinah	Ministère de la Santé	TOGO
Audibert	Céline	MMV	SWITZERLAND
Awor	Phyllis	Makerere University School of Public Health	UGANDA
Ba	Inessa	Clinton Health Access Initiative	BURKINA FASO
Bahari-Tohon	Zilahatou	USAID/PMI	NIGER
Bangoura	Lamine	USAID/Guinea	USA
Barat	Lawrence	Impact Malaria/PSI	USA
Barber	Caroline	Transaid	UK
Barnes	Karen	University of Cape Town	SOUTH AFRICA
Batienon	Philippe	The RBM Partnership to End Malaria	BURKINA FASO
Bechio	Stephane	PMI	CÔTE D'IVOIRE
Bediako	Hope	Freelance	GHANA
Billingsley	Christie	President's Malaria Initiative	ZIMBABWE
Boateng	Paul	Ghana Health Service	GHANA
Bonnenfant	Yung-Ting	USAID	USA
Booi	Khumbudzo	North-West Department of Health	SOUTH AFRICA
Boulay	Dao	PNLP_Burkina-Faso	BURKINA FASO
Bowen	Anna	CDC	MADAGASCAR
Briand	Anne-Sophie	The Global Fund	SWITZERLAND

Family Name	First Name	Affiliation	Country
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Burri	Christian	SwissTPH	SWITZERLAND
Butts	Jessica	CDC PMI	USA
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Cardao	Rafaela	CHAI	ANGOLA
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Chico	Rita	CHAI	MOZAMBIQUE
Chimusoro	Anderson	WHO	ZIMBABWE
Chirambo	Petros	Medical Care Development International	MALAWI
Chizema	Elizabeth	Zambia EMC/ALMA	ZAMBIA
Ciss	Marie Felicite	PMI	SENEGAL
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Condo	Patrick	USAID	BENIN
Costa	Thiago	PNUD	ANGOLA
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Evina	Elvira	Programme national de lutte contre le paludisme	CAMEROUN
Fambe	koffi kunale	Eloquence School of Languages	GHANA
Fashanu	Chizoba	CHAI	NIGERIA
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Day 2 Attendee list:

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Alade	Joseph	National Malaria Control Program	LIBERIA
Ali	Doreen	Ministry of Health	MALAWI
Alpha	Raymond	Population Services International	SIERRA LEONE
Amadou	Hamadou	Chemonics Inc	CAMEROUN
Amutuhaire	Maureen	Ministry of Health	UGANDA
Awor	Phyllis	Makerere University School of Public Health	UGANDA
Ba	Inessa	Clinton Health Access Initiative	BURKINA FASO
Bahari-Tohon	Zilahatou	USAID/PMI	NIGER
Barak	Jennifer	UNICEF	KENYA
Barber	Caroline	Transaid	UK
Barnes	Karen	University of Cape Town	SOUTH AFRICA
Bediako	Hope	Freelance	GHANA
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Bonnenfant	Yung-Ting	USAID	USA
Bowen	Anna	CDC	MADAGASCAR
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Briandt	Angela	Clinton Health Access Initiative	GHANA
Buj	Valentina	UNICEF	SWITZERLAND
Burns	Jordan	USAID/PMI	USA
Burri	Christian	SwissTPH	SWITZERLAND
Butts	Jessica	CDC PMI	USA
Cardao	Rafaela	CHAI	ANGOLA
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Chabuka	Angella	MOH	MALAWI
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Chico	Rita	CHAI	MOZAMBIQUE
Chimusoro	Anderson	WHO	ZIMBABWE
Chizema	Elizabeth	Zambia EMC/ALMA	ZAMBIA
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Ciss	Marie Felicite	PMI	SENEGAL
Coffy	Marlene	The Global Fund	FRANCE
Condo	Patrick	USAID	BENIN
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Ebah	Epole Gwendolyn	Chemonics	CAMEROON
Esch	Keith	PMI Impact Malaria Project (PSI)	USA
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Fomunyam	Tewuh	Chemonics International	CAMEROUN
Gaston	Interpreter	Interpreter	GHANA
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Gitte	Sunil	NIPHTR	INDIA
Gjekete	Prisca Mayeule	OMS	BENIN
Gomes	Marques	MINSA	ANGOLA
Gravata	Arciolanda	USAID	ANGOLA
Green	Cathy	Transaid	UK
Griffith	Kevin	PMI/USAID	USA
Gyasi	Akosua	Jhpiego	GHANA
Halliday	Dale	Unitaid	SWITZERLAND
Halsey	Eric	CDC	USA
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Jagoe	George	MMV	SWITZERLAND
Januari	Obiague	PNLP/MINSAP	GUINEA BISSAU
Joejoe	Miatta Sonkarley	USAID	LIBERIA
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Malpass	Ashley	USAID/PMI	USA
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