Rectal Artesunate Landscaping Assessment Report

Report developed as an output of the Community Access to Rectal Artesunate for Malaria (CARAMAL) project

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Contents

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Glossary

Behavioral Change Communication – Interventions/communication strategies to promote a particular conduct

Cascade training – Step down training from previously trained persons on to another (potentially larger) group of trainees

Case data – information on the incidence of an illness. For example, the number of fever cases

Case management – All activities involved in the handling and treatment of patients

Cerebral malaria – Neurological complication of infection with Plasmodium *Falciparum*

Commodities Demand forecast –A prediction of the expected need for a commodity

Consumption based quantification – Determining need using past consumption data

Continuum of care – Array of healthcare needs over a period of time

Daaras – Islamic Schools in Senegal

Demand Generation – Targeted programs to promote interest and generate demand

Excursion time – Period of time during which products are exposed to temperatures higher than recommended

Expert Review Panel – Independent advisory board of technical experts coordinated by the WHO

Malaria danger signs – Symptoms that indicate a patient has severe malaria

National treatment guidelines – Standards for malaria case management

Operational planning (for quantification) – Consideration of factors such as - time taken for distribution, minimum, stock requirements, re-stocking, frequency etc.- during the quantification process

Post market surveillance – Activities to determine and maintain quality assurance and quality control of products to meet consumer expectations

Pre-referral intervention – Actions and medication given before sending the patient to the next level of care

RAS roll out – Implementation of activities to introduce RAS

RAS scale-up – Implementation of activities to increase the scope and use of RAS

Referral system – Structure for the direction of patients to next level of care required

Seasonal Malaria Chemoprevention - intermittent administration of full treatment courses of an antimalarial medicine to children

Severe malaria – The presence of P. falciparum and one or more malaria danger signs

Stock outs – a situation in which a location has run out of a particular commodity

Stringent Regulatory Authority – Drug regulatory authorities that determine the requirements for pharmaceuticals for human use

Supporting interventions – Intermediations applied to aid an activity over a period of time

Suppository – Medicines for rectal insertion

WHO pre-qualified – Medicines or diagnostics whose manufacturer and manufacturing sites have been screened by the WHO against a pre-determined standard for a specific product

Acronyms

Artemisinin-based combination therapy-ACT
Behavior Change Communication -BCC
Clinton Health Acces Initiative -CHAI
Community Access to Rectal Artesunate for Malaria- CARAMAL
Community health management committees - CHMCS
Community health nurse - CHN
Community health officers - CHO
Community Health Volunteers - CHV
Community health worker - CHW
Community-Based Health Planning and Services -CHPS
Democratic Republic of Congo - DRC
District Health Information Management System - DHIMS2
Expert Review Panel - ERP
Global Fund to Fight AIDS, Tuberculosis and Malaria -GFATM
Global Price Reporting Mechanism - GPRM
Health Center (Centre de Santé) - HC
Health Development Army- HDA
Health Extension Workers - HEWs
Health Post (Poste de Santé) - HP
Health Surveillance Assistants - HSAS
Improving Severe Malaria Outcomes - ISMO
Information, Education and Communication - IEC
Injectable artesunate -Inj AS
Insecticide-treated nets - ITNS
Integrated community case management - ICCM
Integrated Management of Childhood Illness - IMCI
Intramuscular - IM
Intra-venous -IV
Medicines for Malaria Venture - MMV
Management Sciences for Health - MSH
Medicins Sans Frontiers -MSF
National Malaria Control Program -NMCP
National Supply Pharmacy -PNA
Pharmaceuticals Fund and Supply Agency -PFSA
Prequalified -PQ
President's Malaria Initiative -PMI
Programme National de Lutte contre le Paludisme- PNLP

Quality Assured- QA
Rectal artesunate - RAS
Regional Supply Pharmacy - PRAS
Special Programme for Research and Training in Tropical Diseases- TDR
Stringent Regulatory Authority - SRA
Swiss Topical and Public Health Institute - Swiss TPH
The Programme National de Lutte contre le Paludisme - PNLP
United Nations Children's Emergency Fund – UNICEF
Village Clinics – VCs

1. Executive summary

Mortality due to severe malaria particularly cerebral malaria, approaches 100%. With prompt, effective severe malaria treatment and supportive care, this rate drops to 10–20%. Many who fail to receive prompt treatment for severe malaria live in remote settings with long travel times to clinics that can provide the necessary care. Rectal artesunate (RAS) is recommended by the World Health Organization (WHO) as a pre-referral intervention of severe malaria in children under 6 years of age in remote areas, which must be followed by immediate referral to a higher level facility for administration of injectable artesunate (Inj AS) and a course of artemisinin-based combination therapy (ACTs). Until 2015, WHO guidelines recommended the use of RAS for both children and adults. However, in response to new evidence[1], which showed that RAS resulted in higher mortality rates in adults, WHO guidelines were amended in 2015 to recommend the use of RAS only for children below the age of 6 years[2].

Little information exists around which countries have adopted the WHO RAS guidance, nor is much operational guidance available to assist countries planning to introduce or scale RAS. To help address these gaps and generate evidence to inform a successful implementation of RAS, the Community Access to Rectal Artesunate for Malaria (CARAMAL) project, funded by UNITAID, was initiated across select integrated community case management (iCCM) programs in the Democratic Republic of Congo (DRC), Nigeria and Uganda. This landscaping report represents a component of that project. This report aims to provide insights into RAS introduction, its use and its availability across malaria endemic Africa. Information for this report was obtained through a desk review of available information including national malaria treatment guidance, RAS procurement, product information and RAS demand forecasts; combined with visits to countries that operationalized use of RAS and interviews with relevant stakeholders including national malaria control programs, donors and implementing partners.

Key findings presented in this report are:

Adoption of WHO RAS guidelines- Malaria treatment guidelines were found for 38/56 African countries. Of the 38, only 14 have recommendations aligned with the latest WHO treatment guidelines to provide RAS only in children under the age of six, with seven of these countries recommending RAS for age five and below. Of the remaining 24 countries, 13 have RAS in their guidelines but not aligned with WHO guidance (e.g., including usage of RAS in adults or unclear age limitations) and 11 did not have RAS.

[1] 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.
[2] WHO Guidelines for the treatment of Malaria. Third edition. WHO 2015

Available RAS products- Up until 2016, no stringent regulatory authority (SRA) approved RAS products were available: 50mg and 200mg RAS suppositories were available, but were not SRA approved. Donors procuring RAS suppositories used their own QA criteria to assess the quality of the products. In December 2016, the pharmaceutical supplier Cipla obtained Global Fund Expert Review Panel (ERP) approval for its 100mg formulation. This formulation was subsequently WHO prequalified (PQ) in February 2018. An additional 100 mg product formulation, manufactured by Strides Pharma Science Limited (formally Strides Shasun Limited), was ERP-approved in December 2017, and subsequently WHO prequalified in June 2018.

Global RAS procurement- Global annual RAS procurement has varied widely over the last 10 years mainly driven by the procurement of 50mg suppositories. In the absence of any historical consumption or comprehensive data on fever cases, most historic RAS procurements have been guided by quantifications performed using demographic data rather than consumption or case data. The historical annual procurement average of the 50mg suppository (2007 – 2018) is around 312,000 suppositories while that of the 200mg (2008 – 2018) is 201,000 suppositories. With recent procurement volumes included in the forecast model, total demand for RAS in the public sector is expected to grow from 419,000 100mg suppositories in 2017 to 1.7M – 2.8M 100mg suppositories in 2021. Estimated historic demand for RAS in the private sector is expected to remain stable around 2.6 million 100mg suppositories consumed annually.

In country RAS implementation experiences- Good planning and well-functioning health systems were found to be important enablers of a successful RAS roll out. Interventions around 1) training and equipping health workers; 2) sensitizing communities; 3) integrating RAS into iCCM; 4) strengthening referral systems; 5) ensuring high quality care at referral facilities; and 6) using robust quantifications and having an effective distribution network were found to be critical to the adoption and scale up of RAS.

Common challenges found in RAS roll out were: 1) over-quantification, leading to stock expiries; 2) SRA approved RAS products stored at temperatures beyond 30 degrees Celsius (not recommended by manufacturers) resulting in product deterioration; 3) non-SRA approved RAS products sometimes melting during distribution, even under controlled conditions, pointing to potential product quality issues; 4) poor utilization of CHWs trained to administer RAS as a pre-referral intervention reportedly due to poor community sensitization; 5) incomplete referrals post administration of RAS due to the lack of available and affordable means of transportation from the primary to the secondary health facility level; 6) lack of requisite staff and/or treatment at the secondary facilities to provide severe malaria treatment; and 7) poor community health worker (CHW) trainings and/or supervision resulting in low uptake of RAS.

2. Background and purpose

Malaria is one of the leading causes of illness and death in children under-five. A malaria infection may result in a wide variety of symptoms, ranging from absent or mild symptoms such as a headache or a fever to organ failure followed by coma and ultimately death. While the successful scale-up and use of critical commodities such as insecticide-treated nets (ITNs) and Artemisinin Combination Therapies (ACT) have resulted in huge declines in malaria-related mortality since 2000, malaria still results in over 400,000 deaths each year, most of which are in children under 5 years of age and pregnant women[3]. The heaviest malaria burden continues to be in sub-Saharan African countries, accounting for an over 40 percent of malaria cases and over 50 percent of malaria deaths in 2017.[4]

Malaria poses the greatest risk of death within the first 24 hours of experiencing illness. If not treated promptly and effectively, patients' conditions can quickly worsen and become severe. Severe malaria occurs when infections are complicated by serious organ failures or abnormalities in the patient's blood or metabolism. Severe malaria almost invariably leads to death if not appropriately treated. However, with prompt, effective antimalarial treatment and supportive care, severe malaria mortality rates can be substantially reduced. Patients with severe malaria (including infants, pregnant women in all trimesters and lactating women) should first be treated with intravenous or intramuscular artesunate for at least 24 hours until they can tolerate oral medication or parenteral artemether and quinine where injectable artesunate is unavailable. Once a patient has received at least 24 hours of parenteral therapy and can tolerate oral therapy, a full three-day treatment course of ACT must be administered.

Many patients with severe malaria live in remote settings with poor access to formal health facilities. The distance or time required to travel to facilities, the loss of productivity due to time away from work, and the availability and cost of transportation to a health facility all contribute to a patient's inability to promptly seek care, leading to delays in receiving a full and effective course of treatment, increasing the risk of mortality. In these situations, rectal artesunate (RAS) can be an effective pre-referral intervention for young children. RAS rapidly (i.e., within 24 hours) clears 90 percent or more of the malaria parasites and, in children younger than 6 years' old who cannot reach a facility in less than six hours, can reduce the risk of death or permanent disability by up to 50%[5].

The World Health Organization (WHO) recommends administering children younger than 6 years old a single rectal dose of 10mg artesunate per kilogram of body weight. After administering RAS, the child is to be referred immediately to an appropriate facility where follow up care for severe malaria can be provided. The WHO considers RAS to be a feasible and acceptable pre-referral intervention at the community level. While this recommendation by the WHO is classified as "strong," it is based on evidence from only one study[6] and comes with limited operational guidance. There are currently no evaluations of RAS use at the level of community-based health care providers under real-world operational circumstances.

In 2012, UNITAID initiated the Improving Severe Malaria Outcomes (ISMO) project, a Medicines for Malaria Venture (MMV)-led project in partnership with the Clinton Health Access Initiative (CHAI) and the Malaria Consortium, to accelerate demand and adoption of quality-approved injectable artesunate (Inj. AS) in six

[3] World Malaria Report 2018

[4] Ibid.

[5] 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.

[6] Ibid.

countries (Cameroon, Ethiopia, Kenya, Malawi, Nigeria, and Uganda). The project also supported the expedited introduction of quality-assured RAS products in the 100mg dosage developed by the two companies: Strides and Cipla Inc. MMV provided technical assistance for WHO prequalification (PQ) and support to obtain approval through the Global Fund Expert Review Panel (ERP).

In 2017, anticipating WHO prequalification of these RAS products, UNITAID invested in a 3-year consortium project, Community Access to Rectal Artesunate for Malaria (CARAMAL), to support wide scale roll out of RAS. The consortium is led by CHAI, together with UNICEF and the Swiss Tropical and Public Health Institute (Swiss TPH), and supported by MMV and the WHO. Local research partners include the Makerere School of Public Health in Uganda, the Ecole de Santé Publique in the Democratic Republic of Congo, and Akena Research, Evaluation and Consulting in Nigeria.

As part of the CARAMAL project, MMV also launched the Severe Malaria Observatory (https://www.severemalaria.org/) to bring together multiple resources as a repository of information related to severe malaria. Its objective is to deepen the global awareness and knowledge of severe malaria; available severe malaria tools (i.e., job aids) and ongoing severe malaria activities (i.e., studies). The observatory website includes information on RAS and provides a mechanism for sharing evidence and lessons learned through the CARAMAL project. The platform is currently accessed by nearly 2000 people every month.

The CARAMAL project consists of operational research in three focus countries: DRC, Nigeria and Uganda. The project examines how reductions in severe malaria case fatality can be achieved under real-world conditions by introducing RAS through established integrated community case management (iCCM) platforms within targeted communities along with a minimal package of supporting interventions. Evidence gathered through the project will provide valuable information on how community-based delivery of RAS can be implemented safely, effectively, and efficiently to save lives in remote, highly endemic communities.

The CARAMAL project also aims to provide a consolidated overview of experiences from some African countries that have adopted and/or deployed RAS to-date, as described in this landscape document. This document identifies considerations for national malaria program managers and other malaria stakeholders planning to introduce or support the scale up of RAS. The assessment includes the following sections: (1) a review of current guidelines across all African countries; (2) an overview of funding sources for RAS and its suppliers; (3) a quantitative overview of historic and expected RAS procurement volumes; and (4) a description of how RAS is being used in selected countries that have already introduced or adopted RAS as a pre-referral intervention for severe malaria.

3. Methods

The landscape assessment was conducted from September 2017 to April 2018. The assessment included two phases: 1) a desk review of available policy guidance, procurement information, available suppliers and forecasts of RAS demand in private and public sectors and 2) in-country visits and stakeholder interviews in Ethiopia, Senegal, Malawi, Ghana, DRC and Uganda to obtain a comprehensive understanding of each country's experience in procurement, distribution and use of RAS in community health systems. Underpinning these two

phases were multiple interviews, written correspondences and discussions with partners involved in RAS procurement and/or use identified through snowball sampling. A complete list of stakeholders engaged in this assessment is available in Annex 5.

The desk review involved gathering and analyzing available data from all 56 African countries. Based on an analysis of the severe malaria treatment guidelines, countries were divided into 3 categories: 1) "No RAS in guidelines", 2) "RAS in guidelines" (with sub-categories for alignment/non-alignment with WHO guidelines) and "RAS guidelines unknown" (where information on RAS in guidelines was not available). Procurement information was obtained (where available) from President's Malaria Initiative (PMI) and the Global Price Reporting Mechanism (GPRM) for HIV, Tuberculosis and Malaria database hosted by the WHO, Medicins Sans Frontières (MSF) and the United Nations Children's Emergency Fund (UNICEF). The analyses of the guidelines and procurement data were refined based on interviews with CHAIs in-country staff, members of the CARAMAL consortium, and other partners including MMV, WHO, and PMI. Forecast data was pulled from a recent publication by UNITAID; the Global Malaria Diagnostic and Artemisinin Treatment Commodities Demand Forecast, 2017 – 2021. To select countries for in person visits during Phase 2 (Ethiopia, Ghana, Malawi, Senegal), CHAI created an eight-weighted criteria to score, compare, and rank the countries. These criteria included malaria incidence, malaria burden, RAS in guidelines, alignment to WHO recommendations, previous and current procurement/use of RAS and whether or not countries planned to produce RAS in 2017 (Please refer to annex 2 on country evaluation criteria and corresponding weights). In preparation for the country visits, standardized and country specific questionnaires were created to compile information on RAS use. The questionnaire included a mapping of relevant in-country stakeholders that could provide the necessary insights and clarity to questions unanswered through desk research. (See Annex 3 for complete questionnaire used during interviews). Face-to-face interviews were conducted with in-country stakeholders during in-country visits conducted between December 2017-March 2018.

4. RAS Guidelines and adoption

a. Overview of evidence and WHO guidance for RAS

The initial WHO RAS guidance was informed by various studies: A study conducted in Papua New Guinea in 2003-2004, compared the effect of artesunate suppositories to IM artemether in children and adults (RAS: n=41, IM artemether: n=38)[7]. Children receiving RAS experienced more rapid declines in procalcitonin levels (a biomarker for P. *Falciparum*) than those receiving IM artemether. RAS also demonstrated a 90% decline in parasite load across both age groups. In 2009, with support from the Special Programme for Research and Training in Tropical Diseases (TDR), hosted by the WHO, a multi-country study[8] across Africa and Asia randomized over 12,000 children with suspected severe malaria to receive either a single artesunate dose (n=6072) or placebo (n=5996) suppository. All children were referred to the nearest clinic where available injectable treatment could be provided. The researchers found that among artesunate receiving patients who arrived at a clinic after more than 6 hours (the recommended time to get referred, n=1566), 50% had arrived after more than 15 hours. In this group, administering pre-referral rectal artesunate significantly reduced the

[7] Karunajeewa HA, Reeder J, Lorry K, et al. Artesunate Suppositories versus Intramuscular Artemether for Treatment of Severe Malaria in Children in Papua New Guinea. Antimicrobial Agents and Chemotherapy. 2006;50(3):968-974. doi:10.1128/AAC.50.3.968-974.2006.

[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.

"*risk of death or permanent disability compared to those receiving a placebo by up to 50% (risk ratio (RR) 0·49 [95% CI 0·32–0·77], p=0·0013)".* The authors therefore concluded that, "*If patients with severe malaria cannot be treated orally and access to injections will take several hours, a single inexpensive artesunate suppository at the time of referral substantially reduces the risk of death or permanent disability*." However, the study found that rectal artesunate was associated with more deaths in older children and adults (n=4018, RR: 2.21 [95% CI 1.18-4.15])[9][10]. Although there was no conclusive explanation for these trends in mortality, the research did not support RAS use in these older age groups[11]. Two other studies found there were no adverse effect of RAS on adults[12] [13].

Based on these results, WHO issued its first guidance on the use of RAS for adults and children in 2006, followed by three subsequent revisions:

- **In 2006**, WHO introduced treatment guidelines for the use of RAS as a pre-referral intervention for severe malaria for children as well as adults[14].
- **In 2010,** WHO reiterated its guidance to recommend the use of RAS for both children and adults. These guidelines indicated pre-referral intervention with RAS in situations where parenteral medication is not possible and referral is expected to take more than 6 hours[15].
- **In 2015**, the WHO issued refined guidelines for the treatment of severe malaria, recommending that, in situations where intramuscular (IM) injection of artesunate, artemether, or quinine are not available for the treatment of suspected severe malaria, children less than 6 years old should receive a single rectal dose (10mg/kg bw) of artesunate (*WHO Classification: Strong recommendation, moderate-quality evidence*) and be referred immediately to an appropriate facility where the full management of severe malaria can be provided[16].
- **In 2017,** The WHO released an information note that revised previous RAS dosing and recommended that in places with limited diagnostic capacity for severe malaria, RAS should be administered to children under the age of 6 years[17]. It further notes that children with suspected severe malaria between 2 months to 3 years of age should receive one 100mg RAS suppository, and children between 3 to 5 years of age, should receive two 100mg RAS suppositories, by community health workers before referral. The note also highlighted considerations for the implementation and correct use of RAS, emphasizing aspects such as the narrow window of indication and the need for immediate referral, treatment with IM or intra-venous (IV) artesunate at the higher level facility, and completion of a full course of treatment with an ACT once tolerated.

[9] Okebe J, Eisenhut M. Pre-referral rectal artesunate for severe malaria. Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD009964. DOI: 10.1002/14651858.CD009964.pub2.

[10] Although there was no conclusive explanation for the increased mortality in these age groups, researchers concluded RAS should not be used in older children and adults.

[11] Okebe J, Eisenhut M. Pre-referral rectal artesunate for severe malaria. Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD009964. DOI: 10.1002/14651858.CD009964.pub2.

[12] Krishna S et al. Bioavailability and preliminary clinical efficacy of intrarectal artesunate in Ghanaian children with moderate malaria. Antimicrobial Agents and Chemotherapy, 2001, 45:509–516

[13] Barnes KI et al. Efficacy of rectal artesunate compared with parenteral quinine in initial treatment of moderately severe malaria in African children and adults: a randomized study. Lancet, 2004, 363:1598–1605

[14] WHO Guidelines for the treatment Guidelines of Malaria. First Edition. 2006

[15] WHO Guidelines for the treatment Guidelines for Malaria. Second Edition. 2010

[16] WHO Guidelines for the treatment of Malaria. Third edition. WHO 2015

[17] WHO Rectal artesunate for pre-referral treatment of severe malaria. Information Note. 2017

Both iCCM and Integrated Management of Childhood Illness (IMCI) programs have adapted their manuals to reflect the 50, 100 and 200mg dosages (Figure 1,2). Both algorithms only provide guidance for treatment of children under 5 years of age, and do not provide any guidance for treatment of kids between the ages of 5 and 6.

Figure 1: Guidelines on RAS dosing as seen on the Sick Child Recording Form of the WHO CHW iCCM manual: Pre-referral artesunate treatment of childhood malaria in the community.

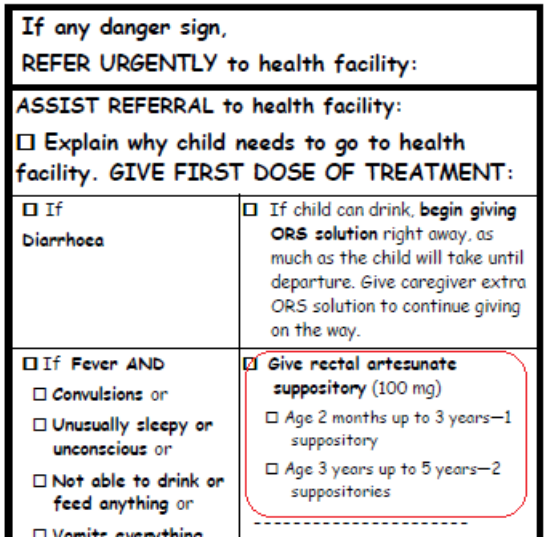


Figure 2: Guidelines on the dosage of RAS in WHO's Integrated Management of Childhood Illness: distance learning course (2014).

AGE or WEIGHT	RECTAL ARTESUNATE SUPPOSITORY	
	50 mg suppositories Dosage 10 mg/kg	200 mg suppositories Dosage 10 mg/kg
2 months up to 4 months (4 - <6 kg)	1	
4 months up to 12 months (6 - <10 kg)	2	
12 months up to 2 years (10 - <12 kg)	2	-
2 years up to 3 years (12 - <14 kg)	3	1
3 years up to 5 years (14 - 19 kg)	3	1

b. Early adoption

Donors and partners including the President's Malaria Initiative (PMI), the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), UNICEF, and MSF started procuring small quantities of RAS for pilot programs as early as 2009[18]. Since then, a review of available RAS procurement data shows that global procurement has remained relatively small, suggesting that RAS has not been widely adopted and scaled across malaria endemic countries. At a high level the following explanations emerged from interviews:

- **Lack of a commercially available, quality-assured product:** Until 2017, only rectal 50mg and 200mg suppository formulations of RAS had been available. These products had neither been quality assured (QA) through a stringent regulatory authority (SRA) nor WHO Prequalification (WHO PQ). In December 2016, a Global Fund ERP approved the first RAS product for a 12-month time-limited approval awaiting finalization of the ongoing WHO prequalification review, thus allowing procurement of RAS using Global Fund grants.[19] In early 2018 the first 100mg RAS product (Cipla) was pre-qualified.
- **Lack of or out-of-date national treatment guidelines for severe malaria:** Until 2014-15, many countries did not have comprehensive guidelines on the treatment of severe malaria. Where treatment guidelines

[18] Based on available data

[19] https://www.mmv.org/access/products-projects/rectal-artesunate-ras

were in place, programs had not always updated them to align with the latest WHO recommendations on RAS use as per the 2015 Guidelines for the Treatment of Malaria (3rd edition).[20]

- **Lack of operational guidance on appropriate use of RAS:** Guidance has not always been available on how to ensure high quality care by community health workers (CHWs), strength of referral systems, and quality of severe malaria management at referral facilities. The potential for misuse of RAS as a monotherapy in the absence of strong systems to provide follow up care with IM or IV artesunate and subsequently, an ACT, or the inappropriate use of RAS as an intervention for uncomplicated malaria have raised concerns about the development and spread of artemisinin resistance.
- **Product characteristics:** Currently, RAS products on the market only provide guidance on storage conditions in temperatures up to 30°C, leaving unresolved questions about product stability at temperatures above 30°C[21]. Reports of melting RAS suppositories have been common.

c. Current national RAS guidelines

A review of 38 available national malaria treatment guidelines found that only 48% (27 of 56) of African countries included RAS (Figure 1) as pre-referral intervention for severe malaria. Only 14/27 countries included RAS in their guidelines in alignment with the latest WHO treatment guidelines. 13 countries have RAS included with outdated guidance for patients above six years old and 11 countries did not have RAS included at all.

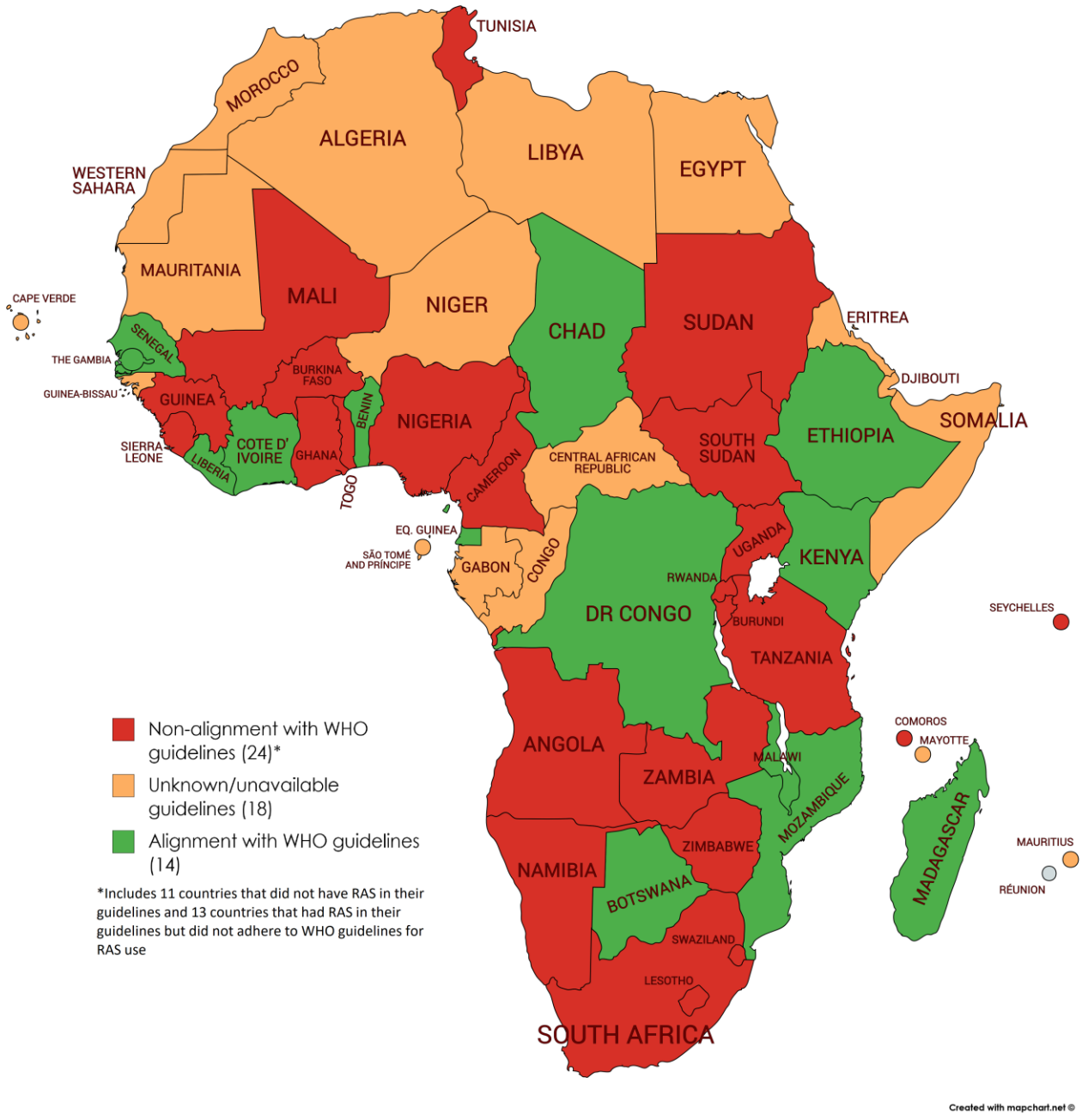
There is limited information about RAS use in communities either as part of existing iCCM programs and/or indicated for use by community health workers. Extensive communication with PMI and UNICEF revealed that many countries do not have community health workers, RAS administration can be limited to peripheral facilities and adoption of iCCM guidelines is varied. Based on the available information, 40 countries have community health worker cadres and only five of these explicitly support RAS administration by community health workers.[22] 31 countries have ICCM programmes; however, official RAS inclusion in iCCM guidelines was found only for Ethiopia.

[20] Guidelines for the treatment of malaria – 3rd edition. WHO 2015

[21] Senegal conducted limited post market surveillance of RAS and found the product to be stable at temperatures up to 40°C.

[22] Documents substantiating RAS use among community health workers were available for only five countries: Ethiopia, Ghana, Malawi, Mozambique and Senegal

Figure 3: Countries that have approved RAS in their National Treatment Guidelines.



5. Supplier and donor landscape

RAS Manufacturer history up until 2016

In 1996, WHO TDR recognized a need for non-oral pre-referral intervention for severe malaria and initiated the development of RAS together with a Swiss manufacturer, Mepha Pharma. WHO TDR completed Phase I, II and III RAS trials in 1997, using the Mepha 50mg and 200mg RAS capsules. Experience from these trials[23],[24] and findings from subsequent studies[25] made it clear that dosing by weight using the existing 50mg and 200mg RAS dosages was not practical, due to dosing issues for children below 6 years of age. Therefore, WHO TDR decided in the late 1990s to simplify the dosing recommendation to 100mg for children.

The updated dosing recommendations did not alter the available dosing strengths. In addition to Mepha Pharma, Bliss GVS Pharma (India) also started manufacturing RAS products of 50 and the 200mg. Neither of these products obtained SRA approval or WHO PQ status. Yet, given the lack of alternatives, countries, donors and NGOs that had introduced or funded RAS relied on these products up until 2014: UNICEF and MSF procured from Mepha Pharma (now called Acino International AG). PMI procured from both Acino and Bliss GVS Pharma until 2014[26]. Annex 1 includes more information regarding historical procurements by country and donor agency.

Two key factors led to a halt in RAS procurements after 2014. First, in 2014, a multi-donor-agency taskforce revised its QA policy to restrict donors from procuring any anti-malarial products that were not yet SRA approved[27]. Second, in 2015, Acino reported quality challenges with heat stability and subsequently halted RAS production altogether. By 2015, most RAS available in countries was procured in or before 2014 and approaching expiry. Together, these factors effectively stopped both production and funding of RAS, though some countries continued to procure RAS up until 2016[28] from a batch manufactured by Acino in 2014 or from other non-SRA approved manufacturers.

Overview of current suppliers and products

The shortage of RAS in 2015 combined with the need for a quality approved product that would align with the new WHO dosage guidelines (i.e., 100mg RAS suppositories) resulted in a request for proposals by MMV for manufacturers interested in obtaining support to develop a RAS product that could be expedited to achieve WHO PQ status. Six manufacturers submitted proposals and two – Cipla and Strides – were selected. In December 2016, Cipla's 100mg formulation became the first quality assessed RAS product under the Global Fund ERP mechanism. The product was subsequently WHO prequalified in February 2018. An additional product,

[23] Krishna S et al. Bioavailability and preliminary clinical efficacy of intrarectal artesunate in Ghanaian children with moderate malaria. Antimicrobial Agents and Chemotherapy, 2001, 45:509–516

[24] Barnes KI et al. Efficacy of rectal artesunate compared with parenteral quinine in initial treatment of moderately severe malaria in African children and adults: a randomized study. Lancet, 2004, 363:1598–1605

[25] Karunajeewa HA, Reeder J, Lorry K, et al. Artesunate Suppositories versus Intramuscular Artemether for Treatment of Severe Malaria in Children in Papua New Guinea. Antimicrobial Agents and Chemotherapy. 2006;50(3):968-974. doi:10.1128/AAC.50.3.968-974.2006.

[26] Correspondence with PMI on 8 November 2017

[27] Conversation with WHO on Dec. 5 2017

[28] Senegal procured RAS in 2016

Strides' 100mg formulation was ERP approved in December 2017, with a validity until December 2018, and received WHO prequalification in June 2018.

In country registration of Cipla's QA RAS product (100mg) has been achieved in Benin, Senegal, Democratic Republic of Congo (DRC) and Republic of Congo. Registration of Strides' product has been achieved in Chad, Gabon, Republic of Congo and DRC. Table 1 describes the key product characteristics as published by the manufactures on their website.

Table 1: Recommendations on RAS product use of Cipla and Strides

Shelf life	**Note for CHWs**
24 months	From Patient Information Leaflet issued by the manufacturer: Do not freeze or refrigerate. Do not store above 25°C. Avoid excursions above 30°C

6. Historical and future global procurement

An analysis of procurement data extracted from the GPRM database, and known RAS donors (i.e., IDA Health, Mission Pharma (MP), GF, MSF, PMI and UNICEF) shows that over 5.5 million RAS suppositories have been procured between 2007 and 2017. A breakdown by country is shown in Figure 4a below of 50 mg RAS suppositories.[29] In figure 4b, a breakdown is provided of the 200 mg RAS suppositories.

[29] Donor sources have been aggregated for confidentiality reasons.

Figure 4a: Historical procurement of 50mg RAS, 2009-2018

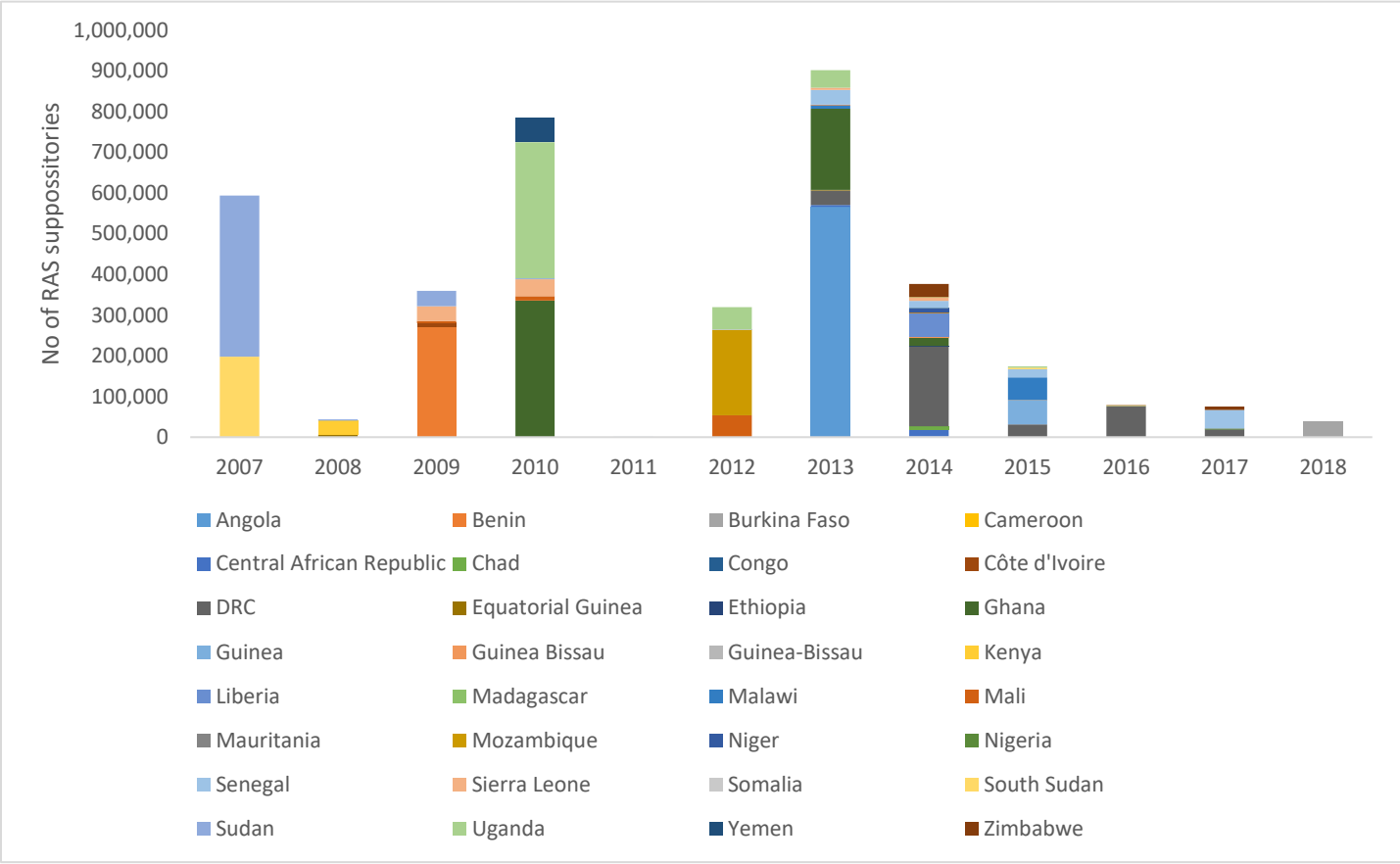
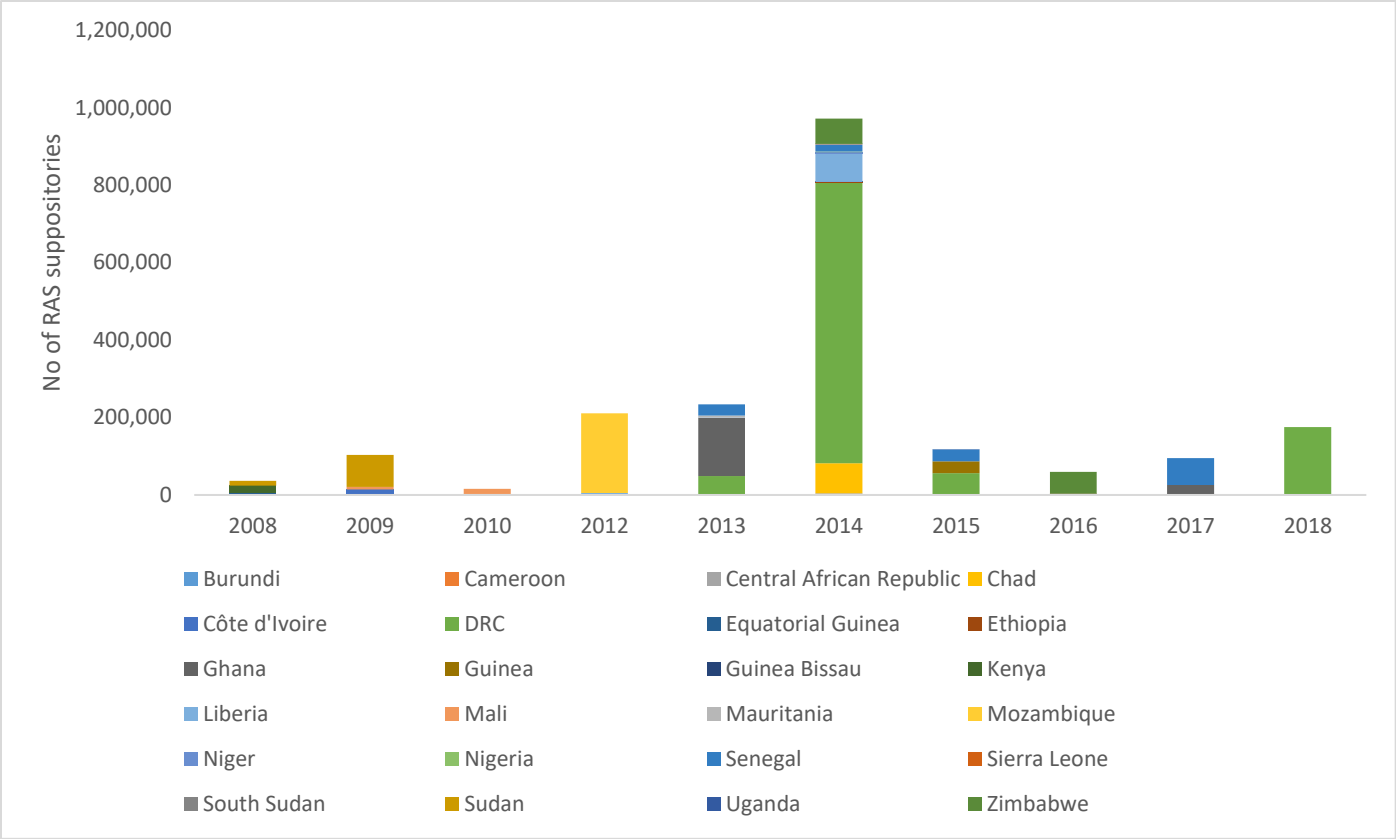


Figure 4b: Historical procurement of 200mg RAS, 2009-2017



The average price of a RAS suppository (2 tablets/pack) has varied between $0.28 and $0.47 for the 50mg suppository, and from $0.52 to $0.72 for the 200mg suppository, as depicted in Figure 5. Given these prices, the cost of treatment for children under the age of 3 ranged from $0.28 to $0.54 while the cost for children 3 – 6 years old ranged from $0.56 to $1.08 as depicted in Figure 6.

Figure 5: The yearly average price of a RAS suppository by dosage according to the WHO GPRM database (accessed 24/08/2017).

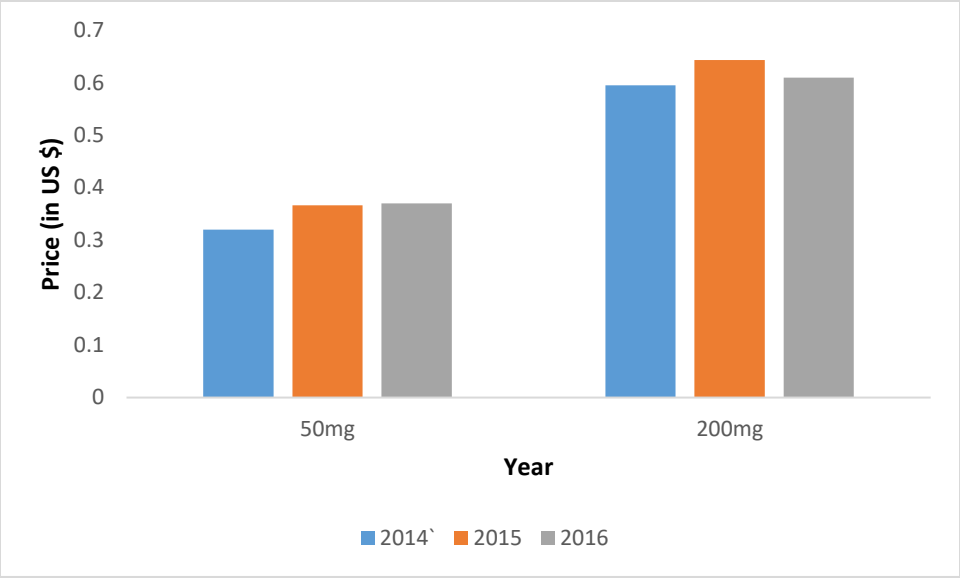
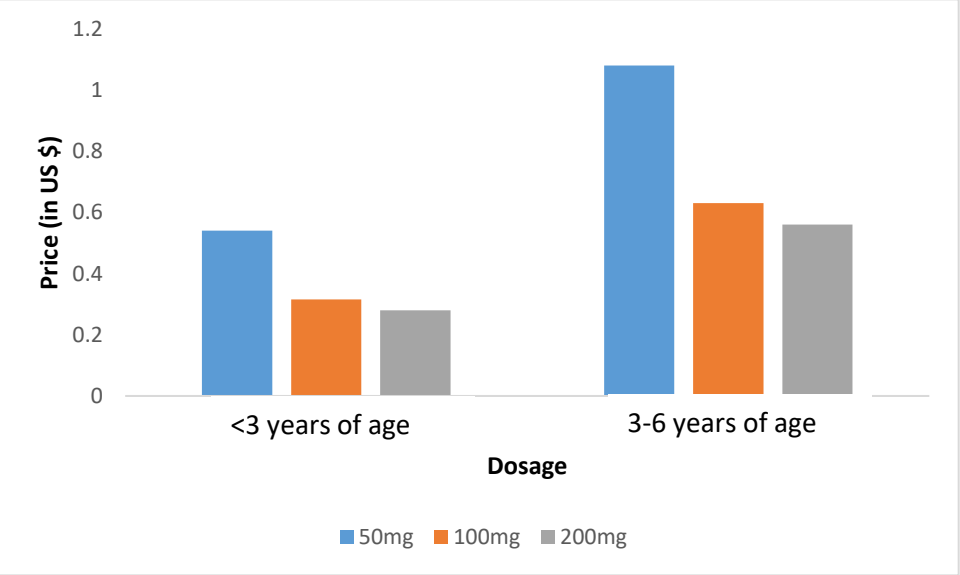


Figure 6: The yearly average price of RAS per treatment as recorded in the WHO GPRM database (accessed on 01/06/2018) for children below 6 years of age



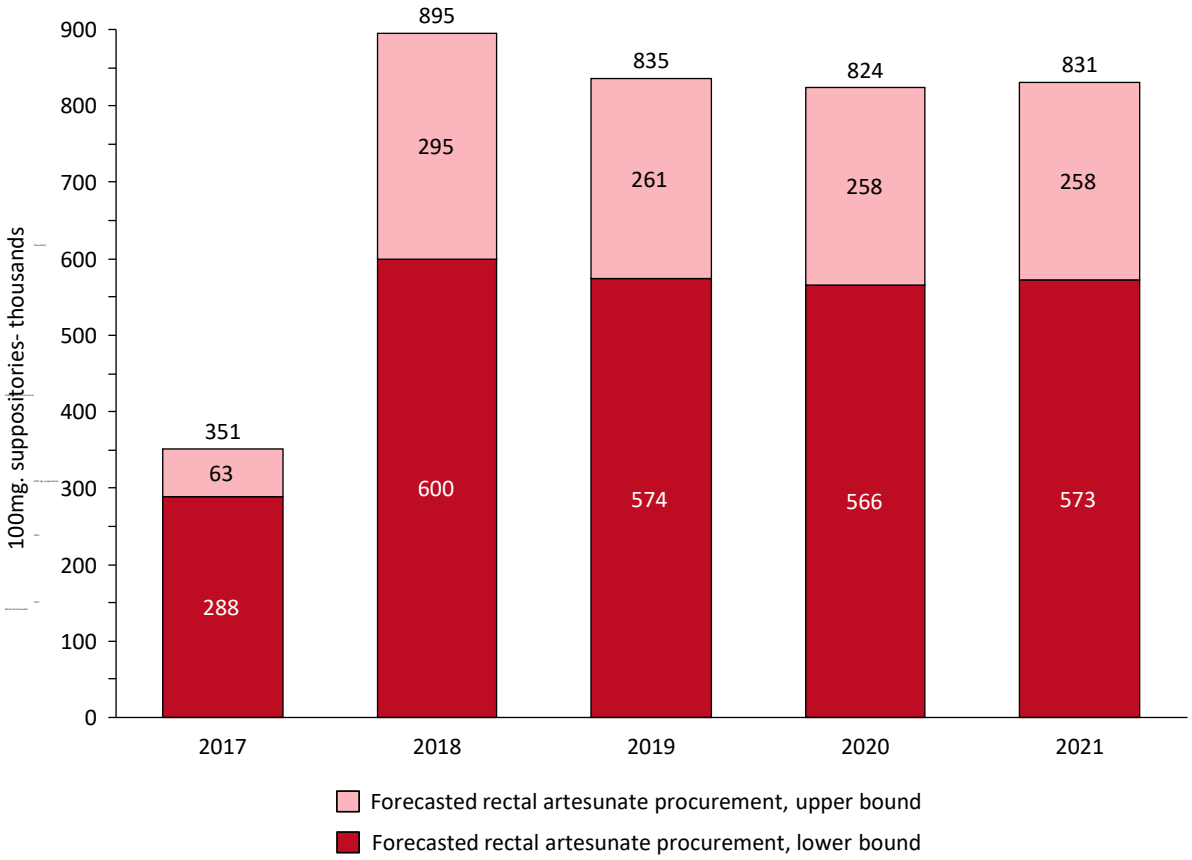
UNITAID's Global Malaria Diagnostic and Artemisinin Treatment Commodities Demand Forecast for 2017-2021 estimates that public sector procurement of quality assured 100mg RAS suppositories will increase from 288,000 in 2017 to 573,000 in 2021[30] [31] (Figure 7). Our review also found that that, in 2018, PMI is planning to procure RAS in several African countries including Burkina Faso, DRC and Madagascar, while GFATM funds will be used to procure RAS in DRC, Nepal, Kenya, Mali, Guinea Bissau and Yemen.

[30] Global Malaria Diagnostic and Artemisinin Treatment Commodities Demand Forecast, 2017 – 2021, UNITAID, 18 December 2017

[31] These estimates were based on assumptions that 1) the 29 countries that currently have established guidelines for use of RAS will adopt and scale RAS over the next few years, and 2) that the volumes these countries will procure will be in proportion to their projected procurement volumes of injectable AS.

Data around private sector use of RAS is extremely limited. The aforementioned forecast report projects private sector RAS demand to remain constant around 2.5-2.6 M 100mg suppositories between 2017-2021.[32] This estimate is based on actual manufacturer sales to malaria endemic countries from IMSHealth (an international health care market intelligence firm now known as IQVIA).

Figure 7: Forecasted public sector procurement for RAS for the 100mg dosage, 2017 – 2021. Figure taken from UNITAID report *"Global Malaria Diagnostic and Artemisinin Treatment Commodities Demand Forecast, 2017 – 2021" (2018)*[33]



[32] Global Malaria Diagnostic and Artemisinin Treatment Commodities Demand Forecast, 2017 – 2021, UNITAID, 18 December 2017
[33] Ibid.

7. Country experiences with RAS introduction and use

Interviews with relevant stakeholders were conducted in six countries with prior history of RAS procurement and roll-out: Ethiopia, Ghana, Malawi, Senegal, DRC, and Uganda. In each of the countries, lessons learnt and challenges were identified, laid out in country sections below.

a. Democratic Republic of Congo (DRC)

The burden of malaria is extremely high in DRC. Malaria is responsible for 60,500 deaths annually[34] or 18% of the under 5 deaths in DRC[35]. The country has trained CHWs who perform basic diagnosis and follow treatment protocol for uncomplicated malaria, diarrhea and pneumonia, subsequently referring patients to the health centers. Due to the often-long distance between villages and medical facilities where severe malaria can be properly treated, the introduction of RAS has been considered a significant opportunity to reduce malaria deaths in DRC. In 2012, DRC updated its malaria treatment guidelines to include the use of RAS for the pre-referral intervention of severe malaria and recommend RAS use only in children younger than five to reduce the risk of complications and death from malaria.

DRC's RAS experience started with a USAID funded project, implemented by Management Sciences for Health (MSH), which studied the feasibility and acceptability of using pre-referral intervention at 51 community care sites across 7 health zones in 4 provinces – Kasai Central, Lomami, Kasai Oriental, and Lualaba between August 2014 and June 2016. The study found that the introduction of pre-referral intervention increased community health workers' ability to identify severe malaria danger signs, and that high referral adherence rates were achieved among those receiving care.[36]

Following the USAID funded RAS study, RAS was included in the country's iCCM guidelines in 2012. Over the course of the next 14 months, trainings of community health workers and their supervisors were conducted, including refresher trainings. CHWs were also given practical training on how to insert a suppository in the under 5 patient group. DRC initially procured the 50mg and 200mg formulations of RAS. Recently, both Cipla and Strides brands were registered and can be imported. Quantification for malaria commodities was performed by the Programme National de Lutte contre le Paludisme (PNLP) with support from partners; Chemonics and Sanru. Both PMI and GFATM funds have been used to procure RAS over the last few years. Little information is available about the scale and success of the RAS roll out in DRC but interview findings suggest that RAS stock outs at the community level were common and that many CHWs were not actually trained to administer RAS.

Challenges (found in the USAID/RAS Study)

1. Supply chain challenges: At the community care sites, supply chain challenges were common, resulting in stock-outs, particularly of the 50mg RAS product.
2. Dosage issues: As the 50mg RAS product was stocked out, only the 200mg RAS product was available at the study sites. This meant that only children over above 12 months of age were able to be administered with RAS.
3. Incomplete referrals: Treacherous terrain in the rainy season made it difficult for both the research teams as well as patients and their care givers to journey to the relevant sites for pre-referral intervention with RAS.

[34] World Malaria Report 2017
[35] Lives Saved Tool 2012
[36] Evaluation de l'utilisation du traitement de pre-reference du paludisme grave dans les sites des soins communautaires en RDC 2016

Lessons learnt (from the USAID/MSH Study)

1. Integration into iCCM: The USAID study found that integrating pre-referral intervention for severe malaria into iCCM at the community-based sites significantly improved the chances of successful introduction of RAS.
2. Strong advocacy: There is a need to push for community and health worker sensitization, as well as behavioral change communication (BCC) to both promote the knowledge and awareness of the danger signs for malaria, while also increasing recognition of the use of RAS as pre-referral intervention in order to gain acceptance of this intervention.
3. Strong referral system: Strong referral systems are imperative for the survival of children put on RAS including an affordable means of transportation to ensure that patients administered with RAS are able to reach the health facility for further care and treatment.
4. Good training and supervision of CHWs: Capacity building at the CHW level is necessary to ensure clients with danger signs are immediately identified.

b. Ethiopia

There are an estimated 2.6 M (range 0.6 – 5.8 M) malaria cases annually in Ethiopia and 69% of its population is at risk of infection[37]. Children below 6 years of age account for 8,353 cases annually. There were 510 malaria deaths reported in 2017, with deaths in children under 5 decreasing from 46 to 12 between 2013 and 2016[38].

With support from PMI, Ethiopia reviewed its national treatment guidelines and introduced RAS for the pre-referral intervention of severe malaria in 2012. Two dissemination approaches were used to ensure that staff were well trained on the revised guidelines: first, two-day cascade trainings were performed on the revised guidelines at the regional, zonal and district health offices levels. Second, iCCM trainings incorporating RAS were rolled out nationwide, covering 17,000 health extension workers (HEWs) stationed at health posts, and 3,000 supervisors at the health centers.

Interviews with stakeholders revealed that RAS was well-received for use in children but that most adults preferred alternative modes of administration such as IM or IV routes for treatment. The uptake of RAS in children but not in adults, prompted Ethiopia's MOH to align its treatment guidelines with WHO guidance to recommend RAS only for children below 6 years of age in their 2016 guidelines. Currently, RAS is dispensed at the government health center and health post levels through HEWs. Volunteer members of the community who constitute the health development army (HDA) support HEWs in liaising with community members and provide referrals from the community to the health post.

The RAS product Ethiopia imported and used in 2012 (specific product not known), was said not to be registered at the time but had received a waiver. Quantification was originally done by the Pharmaceuticals Fund and Supply Agency (PFSA) using service (number of pediatric severe malaria patients seen) and demographic data. 36,000 packs of 50mg RAS suppositories (6 suppositories per pack) and 72,000 packs of 200mg RAS suppositories were procured. Quantification changed in 2017 when only case data was used. Buffer stock and wastage were included in the forecasts. The original procurement in 2012 of 50mg and 200mg RAS formulations

[37] WHO World Malaria report. 2017.

[38] It is important to note that the exact number of malaria deaths is uncertain as most deaths are categorized by the clinical cause (e.g., severe anemia), rather than "malaria" per se.

was distributed across 10,500 health posts in the endemic areas in northern Ethiopia as part of the iCCM drug kits. However, at the time of the visit in 2017, Ethiopia was stocked out of RAS.

Challenges observed

1. Low initial uptake: Despite national and sub-national trainings, low uptake of RAS was observed in 2012-13. Low uptake may have been driven by a lack of demand for RAS. Many adults preferred to take alternative treatments, and it was reported that many mothers, recognizing their child's severe disease, went straight to health centers for treatment instead of the primary health posts. The expansion of health centers in Ethiopia at that time may have contributed to a lack of care seeking at the health post level for severe disease.

2. Inaccurate quantification: Due to the absence of historical consumption data on RAS and the difficulty of estimating the number of severe malaria cases under 6 that would require RAS, the RAS need may have been over quantified (quantification accounted for ~20,000 cases).

3. Distribution challenges: At the time of the first procurement, RAS was not yet part of the iCCM supply chain (i.e. the iCCM drug kit). As a result, distribution and excursion time for RAS to reach health posts was quite long (a few months), reducing its shelf life.

4. Temperature stability: Temperature of storage conditions at health posts was not monitored and anecdotal field reports suggest that RAS often melted at health post level. In addition, there were reports of the product melting at the PFSA warehouse and while in the distribution chain, even where the product was transported in a controlled environment which pointed to potential product quality issues.

5. Weak referral system: While there is a referral system in place from the community to the health post, referrals are not tracked by the HDA or HEW to ensure that children referred from the community make it to the health post for pre-referral intervention or that children from the health post make it to a health center for administration of Inj AS and ACTs.

Lessons learnt

1. Advocacy: While health care providers at different levels were sensitized to RAS and its uses, weak onward communication to caregivers meant that caregivers rarely took severe cases to the health posts where RAS was available. Increasing accessibility of health centers (where Inj AS could be administered) to the community may also have influenced this behavior. Improved education of caregivers regarding RAS availability may help improve its uptake especially in communities still distant from health centers.

2. Product handling: Many areas in Ethiopia have temperatures greater than 25^{o}C (i.e., temperatures can reach 40^{o} to 45^{o} C). Available guidance on the Cipla product indicates an 18-month shelf life (including transport time) in storage conditions between 24 and 30^{o}C. Hence, it is important to ensure that RAS is transported and stored under manufacturer specified temperature ranges to prevent deterioration of product quality.

3. Product quality: The RAS product procured may have melted at PFSA central warehouse and during distribution. Because temperature is controlled at central and regional warehouses as well as during distribution, deterioration may have represented a product quality issue. Procuring a SRA approved product should be encouraged as well as a need for strong post market surveillance to be able to address any quality issues found in the field.

4. Product quantification: While consumption data is lacking for RAS, the previously used quantification method was simplistic, leading to over quantification of RAS. A certain degree of expiry should be expected for a product that must be kept in reserve for severe disease emergencies, but this need must be balanced with how to use donor funds most efficiently. In addition, some of the operational considerations around distribution were not taken into account. Quantification for RAS should be conducted using a more robust methodology that takes into account as many in-country data sources as possible, as well as the operational planning (time taken for distribution, minimum stock requirements, re-stocking frequency etc.) required to facilitate an effective RAS roll out.

c. Ghana

In 2016, there were over 8M cases reported in Ghana. All of the country's population is considered at risk[39]. From 2012 to 2016, according to Ghana's District Health Information Management System (DHIMS2), malaria cases seen in health facility outpatient departments have remained constant around 300 per 1,000. Under 5 malaria case fatality rates declined from 0.67% to 0.51% between 2013 and 2015.

In 1994, Ghana launched the Community Health and Family Planning Project, which pilot tested four different service delivery models. The most successful model served as the basis for the National Community-Based Health Planning and Services (CHPS). This model was comprised of three components: 1) a physical structure (i.e., a compound)[40] where community health officers (CHOs), who are salaried employees, provide 'easy-to-reach' services; 2) Community Health Volunteers (CHVs), who are non-salaried members of the community, provide community outreach, referrals, and health education; and 3) community health management committees (CHMCs) that oversee community mobilization and provide general support to CHOs and CHVs.

Minimum requirements of a CHO include training as a community health nurse (CHN), certification as a CHO, and one year's experience working in a health center, with 6 months practice in the sub-district or attachment to a practicing CHO. CHOs receive 2 years of training while acquiring their CHN certificate.

RAS was introduced into the national malaria treatment guidelines in Ghana in 2014 recommending RAS as a pre-referral intervention for both children and adults, administered by CHOs. The role of CHVs in malaria case management is limited to diagnosis and referral to CHPS in the community. By policy, treatment for severe malaria, including administration of injectable artesunate, is performed at health centers, though based on the condition of the patient, referral may be made to the district hospital. Injectable artesunate is often procured from the private sector and CHOs administer injectable artesunate at the CHPS compounds, as they have the requisite training.

There are currently plans to revise the national guidelines to align with current WHO guidelines that recommend RAS use for children below 6 years of age.

For 2018-2020, RAS has been quantified for all strengths (50mg, 100mg and 200mg) and all age groups, while the national malaria treatment guidelines are modified to align with WHO recommendations to use only QA 100mg RAS. An assumption was made that 10% of severe malaria cases would receive pre-referral intervention with RAS in order to determine the total number of severe malaria cases requiring pre-referral intervention with RAS. After the initial RAS procurement prior to 2015, no further RAS has been procured and Ghana was stocked

[39] Ibid.

[40] A two-room facility with equipment for basic curative and preventive care

out of RAS for up to 2 years. PMI is funding procurement of 100mg RAS in 2018, with some orders of RAS having already arrived in country in early 2018.

Challenges

1. Alignment of national policy with WHO guidelines: The national RAS policy in Ghana is not aligned with WHO recommendations. While it is known anecdotally that in practice, only children under 6 are administered with RAS, non-alignment between policy and practice creates confusion. For example, while the country conducts its national RAS quantification considering both children and adults with severe malaria, donors follow WHO guidelines and only procure quantities sufficient for children under 6.
2. While CHO are allowed to provide RAS, they cannot achieve the same scale of community reach and intervention as CHV. CHV, however, are not allowed to provide RAS and this limits the reach and timeliness of much needed pre-referral intervention as patients first have to reach a CHPs compound.

Lessons learnt

1. Alignment of national policy with WHO guidelines*:* The national RAS policy in Ghana must be updated and aligned with WHO recommendations to facilitate procurement of commodities by donor agencies and ensure case management services are provided based on the most up to date guidelines.

2. Skilled staff at community level: CHPS compounds in Ghana are staffed by paid employees of the Ghana Health Service with the requisite training to manage severe malaria including administration of RAS and Inj AS. Other countries should consider staffing health facilities in the community with trained staff that has the technical capacity and training for to manage severe malaria.

3. Cheap and accessible transport: Public transport in Ghana is inexpensive and accessible. CHOs are also equipped with bikes to transport patients from the CHPS compounds to health centers or districts hospitals, which has enabled successful completion of referrals and treatment.

d. Malawi

There were an estimated 4.5 M malaria cases in Malawi in 2016 and all of its population is considered at risk [41]. In 2013, malaria was the leading cause of death for children under the age of five years, accounting for 22% of all deaths of the under-five children.[42] Malaria is also a major cause of admission for children under the age of five years in Malawi,[43] accounting for more than half of all admissions to hospitals.[44]

RAS was introduced into the national treatment guidelines in July 2013. The guidelines were established based on the most current WHO guidelines at that point, in which RAS was recommended as intervention for both children and adults. Though there are plans to revise the national guidelines to align with current WHO guidelines (limiting RAS use to children younger than six years of age), resource shortages and various other guidelines pending revision have delayed amendment of national treatment guidelines. In practice, adults with

[41] WHO World Malaria report. 2017.
[42] WHO. Malawi Neonatal and child health profile. Geneva: WHO, 2016.
[43] USAID. Evaluation of the Impact of Malaria Control Interventions on All-Cause Mortality in Children under Five Years of Age in Malawi: Malawi Malaria Impact Evaluation Group USA: CDC, 2016.
[44] Government of Malawi. Health management information systems (HMIS). Lilongwe: Ministry of Health, 2010.

symptoms of severe malaria are typically referred directly to the nearest health center to receive Inj AS without being administered RAS as a pre-referral intervention.

In 2014, a pilot project in select hard-to-reach villages in Mchinji district was implemented to integrate RDTs and pre-referral RAS into the iCCM programme[45]. Selected CHWs called Health Surveillance Assistants (HSAs) from hard-to-reach areas received an additional three-day refresher training, which included modules on how to perform RDTs, appropriately treat febrile children based on RDT results, assess for danger signs and administer rectal artesunate. Following this pilot, full implementation of RAS along with mRDTs was rolled out via the iCCM system in mid-2016. The pilot showed a high level of acceptance of RAS.

HSAs, based at Village Clinics (VCs), provide management for uncomplicated malaria and now provide pre-referral intervention with RAS for children under the age of 5. HSAs reside in hard to reach areas, which are areas with difficulties in tele-communication and access to health centers. Village clinics (either a HSA's home in the community or a community-agreed structure such as a church or beneath a big tree) provide dedicated case management services for malaria on select days of the week (usually two days). Depending on the case, VCs also provide management of malaria and SM cases on others days of the week as well. Senior HSAs and clinicians at the health centers administer Inj AS for severe malaria patients.

As of September 2015, over 4500 HSAs in Malawi had received iCCM training and were providing services nationwide at VCs. However, not all HSAs have been trained on administration of RAS. In addition to HSAs, volunteers within the community provide support with sensitization and mobilization. Despite development and dissemination at the community level of health education posters promoting RAS, the practice of skipping the VC and taking a febrile child directly to the health center is common.

Following administration of RAS, a child presenting with severe malaria symptoms at the VC level is given immediate referral advice by the HSA. The child's parent is provided a referral slip and details are noted in the village register. The bi-directional referral slip contains three sections: 1) a part of the slip used by the HSA to report basic patient information; 2) a second part of the slip retained by the health center-level clinician who saw the patient; 3) a third part of the slip returned to the VC HSA to record completion of referral. Follow up on referrals is weak as parents often fail to complete the loop (i.e., fail to return to the VC to hand over the third part of the slip) and HSAs often do not follow up with caregivers. Though ambulances are sometimes available to transport patients, walking serves as the main mode of transportation from VC to health facility. Only an estimated 240 cases completed referral in 2017 for febrile illness from the village clinic to the health center.

The first batch of RAS was procured by PMI in 2015, followed by a donation of 90,000 doses via MMV in 2016. Both supplies were supplied by Acino. PMI plans to procure RAS in 2018. At the national level, quantification is scheduled to take place every two years. Supply chain for malaria commodities at the village clinic level (including for RAS) follows a pull-system, whereby HSAs report stock data on a monthly basis through a mobile phone based system called cStock. In terms of process flow, HSAs inform health centers of their stock status through cStock. The health center consolidates information across VCs in its catchment area and alerts the IMCI office for stock. When stock is re-supplied and ready for collection, the health center informs HSAs. In practice, Malawi has faced chronic supply chain issues, with stock outs occurring at all levels of the health system

[45] Phiri et al. (2016). Feasibility, acceptability and impact of integrating malaria rapid diagnostic tests and pre-referral rectal artesunate into the integrated community case management programme. A pilot study in Mchinji district, Malawi. Malaria Journal. DOI: 10.1186/s12936-016-1237-2

including at the community level. RAS is transported by HSAs from the health center to village clinic on bicycles, exposing RAS to high temperatures. It is known that RAS distributed to village clinics have melted due to this exposure.

Challenges

1. Partly functioning referral system: Although bi-directional referral slips are in place and in use, a significant portion of referrals are either not completed or not reported.
2. Weak training/mentorship: Some HSAs reported feeling uncomfortable administering RAS. A lack of confidence is attributed to (a) a lack of mentorship at the village clinic level on the use of RAS and (b) delays in mentoring or reorienting HSAs on management of pediatric severe malaria cases.
3. Weak advocacy: Parents often skip the village clinic level where an HSA can administer RAS, and instead take the child directly to the health center. Health centers are often very busy, crowded, and over-burdened and may not provide the best quality of service for patients, including urgent pediatric severe malaria cases that have not even received pre-referral intervention.
4. Weak supply chain: Malawi has faced chronic supply chain issues, which have often led to product shortage including shortage of RAS.

Lessons Learnt

1. Capacity building and supply chain: Trainings and Information, Education and Communication (IEC)/ BCC campaigns need to be accompanied by a strong supply chain to ensure regular availability of RAS and strong uptake.
2. Training and supervision: Quality training and regular supervision are key to ensure adherence to guidelines to prevent monotherapy and inappropriate dosage of RAS.
3. Transportation and storage of RAS: RAS must be transported and stored under manufacturer recommended conditions to ensure stock does not melt upon exposure to high temperatures. Ensuring proper guidance and monitoring conditions for transport and storage can prevent such issues.
4. Referrals: As caregivers must take their children by foot from village clinic to HC, the likelihood of incomplete referrals increases. Ambulances are not always available for transport of children with severe febrile illness to the health facility. This gap underscores the importance of ensuring access to affordable means of transport to ensure that referrals are completed while highlighting the need to bring higher quality of care closer to the patient.

e. Senegal

There are over 700,000 malaria cases reported annually in Senegal and all of its population is considered at risk[46]. The 2015 DHS showed that under-five mortality fell from 121 deaths per 1,000 live births in 2005 to 59 in 2015 – a 51 percent drop[47]. Senegal reports few severe malaria cases, potentially due, in part, to a combination of annual seasonal malaria chemoprevention (SMC) campaigns for children up to the age of 9 years and active case detection.

In 2015, RAS was piloted as a pre-referral intervention for severe malaria for children under the age of 5 in two high burden districts – Keneya and Keydougou. After an initial evaluation, RAS was rolled out in three other

[46] Ibid.
[47] PMI Country Profile - Senegal

districts. In 2018, RAS will be scaled to 40 out of 76 high burden districts in the southern, central and western parts of Senegal. Health workers in the pilot districts were trained on the revised guidelines and use of RAS using a cascade approach. Post-market surveillance of RAS was performed in a very limited fashion, wherein a few RAS samples were withdrawn from the field one time and their stability tested. The RAS samples tested did not show product deterioration.

The public health system in Senegal is arranged as a three-tiered structure: hospital level; health center (Centre de Santé) level and health post (Poste de Santé) level. Health posts supervise "health huts" (Cases de santé). Rural health huts are managed by local communities and staffed by one or two trained Agent de Santé Communautaire or community health workers (CHWs), matrones (trained birth attendants) and relais, who are health educators and communicators. Health center and health post staff and CHWs are trained to administer RAS.

Since 2012, active case detection has been conducted as part of home-based management of malaria in the south/south east regions and in the central regions in districts identified as malaria hotspots. During the high malaria transmission period, volunteers perform weekly visits to every household in their villages, actively looking for suspected cases and providing malaria case management including referrals as needed.

In some endemic areas (i.e., Diourbel, Kaolack, and Touba), malaria morbidity and mortality are relatively high. In these areas, many severe malaria cases are typically found in informal residential Koranic schools called Daaras, where living conditions are favorable to malaria transmission and limited resources lead to delayed health care seeking. As a response, the NMCP trained teachers in these schools to act as volunteers to provide basic malaria case management, including RAS.

Senegal's referral system is considered strong. Care seekers receive referrals from CHWs for their children for severe malaria through a referral slip, and arrange to go to the referral facility using their own transport or public transport (relatively strong throughout Senegal). In hard to reach areas, horses or other local modes of transportation are used.

Quantification for RAS is consumption based. Senegal has had a spate of RAS expiries due to a combination of insufficient historical consumption data and inaccurate quantification. The central warehouse of the National Supply Pharmacy (PNA) distributes supplies to Regional Supply Pharmacy (PRAs) which, in turn, supply peripheral structures (health districts, regional hospital and other health structures). District warehouses resupply from PRAs, and supply health posts, health huts and home based care sites.

Challenges

1. RAS expiries: RAS expiries have occurred in Senegal due to inaccurate quantification. The issue of drug expiration is exacerbated by the positive situation of low malaria prevalence in Senegal (health posts often going for a period without severe febrile cases) and the need to maintain a minimum stock of RAS at health center level.

2. Weak post marketing surveillance of RAS product: There are several areas in Senegal (including the 3 districts where RAS has been rolled out) where the temperature routinely surpasses the 30 degrees Celsius threshold recommended by manufacturers. A limited temperature stability study, however, which showed the stability of RAS in the field over 30 degrees, has been used to rationalize RAS use and distribution in areas with high temperatures.

Lessons Learnt

1. Supply chain: Robust quantification and operationally sound distribution plans are required to prevent expiries. At the same time, there needs to be agreement and understanding that a certain percentage of expiries will occur and this percentage must be accounted for in the quantification.

2. Referral systems: Senegal's experience shows that referrals post administration of RAS can be completed successfully. Good public transport and a reliance on local means of transport can help ensure that care seekers have an affordable means of transportation to complete the referral.

3. Customized CHW programs: Senegal successfully customized its volunteer program in the Daaras (Islamic schools) by training teachers in malaria case management, thereby reaching populations that otherwise may not have access to care.

f. Uganda

In Africa, Uganda ranks sixth on the list of countries contributing to annual deaths from malaria. The country has one of the highest transmission rates in the world with approximately 16 million cases reported in 2013 and over 10,000 deaths annually[48]. According to the NMCP, malaria accounts for 50% of health facility outpatient visits and up to 27.2% of inpatient deaths amongst children younger than five.[49] Malaria transmission in Uganda is perennial and children younger than five and pregnant women are usually the most at risk groups.

The Ministry of Health in Uganda has five levels of health services– national, regional, district, sub district (county) and community. The public health sector accounts for 44% of health services and the private sector for 56%.[50,51]. Uganda's iCCM program was launched in 2014 and currently operates in 80 out of 121 districts across the country. Several partners fund the country's iCCM programs, which are implemented in over 60% of the country.[52].

In 2011, Uganda updated its essential medicines list and standard treatment guidelines to include RAS as a pre-referral intervention for severe malaria. The policy recommended use of RAS at the community level and at lower level facilities without the capacity to manage severe malaria. The country does not follow the latest WHO recommendations to use the drug only in children younger than six years of age. There are ongoing consultations to update the guidelines to align with the WHO recommendations.

Following revision of the treatment guidelines in 2011, the NMCP developed guidelines and tools for health workers, conducted integrated management of malaria trainings, supervision activities, social mobilization, and private sector engagement with the goal of ensuring optimal uptake of RAS and other recommended antimalarials. Despite these efforts, Uganda has experienced low uptake of RAS due to the limited scope of training on RAS restricted to certain cadres of health workers as reports of product heat stability issues.

While the current iCCM curriculum includes RAS as a pre-referral intervention for severe malaria, RAS use is in practice, limited to health facility levels II and III by trained nurses and clinicians. RAS is not currently used at the community level and there are no immediate plans to change this. Village health workers at the community level

[48] Severe malaria case management in Uganda. 2018
[49] Malaria Reduction Strategic Plan 2014 - 2020 (UMRSP)
[50] Uganda national household survey 2012/13
[51] MIS 2009
[52] Uganda national malaria control policy 2011

are tasked with diagnosis, treatment and referral of patients within the iCCM program, but not with administration of RAS.

When a severe malaria case is encountered at the community level, it is referred to a higher level facility or to the private sector for treatment. When a referral is to be made to a higher level facility (HCIV and hospitals), the provider fills a referral form and directs the caregiver to a referral facility. There is no ambulatory system to support referral and, as such, caregivers must transport themselves and patient across far distances at their own expense. Logistical costs create a sizeable barrier to receiving adequate care at the referral facilities. In addition, if the patient does successfully make the journey, the higher level facility may have inadequate personnel or a lack of requisite drugs.

The National Drug Authority (NDA) in Uganda has registered and allowed for procurement of 50mg and 100mg RAS formulations, which are not SRA approved. Uganda is currently in the process of registering both the PQ'ed Strides and Cipla products. RAS was initially donated by the Chinese government but has subsequently been procured by the Ugandan government. The Pharmacy Division of Uganda's MOH quantifies national need while the government provides funding to the National Medical Stores (NMS) for procurement. NMS signs contracts with suppliers who then deliver RAS to the NMS. NMS subsequently distributes RAS (along with other commodities and medicines) to targeted facilities based on their annual procurement plans on a bimonthly basis. RAS is stored at the central warehouse and distributed to HC IIs and IIIs. Temperature storage and product quality issues seemed common occurrences; findings suggest that RAS was often found unusable after having melted at high temperatures. In addition, shortages of Injectable artesunate have been observed at referral facilities, leading to the use of quinine for the treatment of severe malaria. Shortages were not attributed to low national stock, but rather to general issues in the supply chain system.[53]

Challenges observed

1. Low uptake:
    - RAS trainings did not reach all health facilities. Trainings that were successfully administered did not have practical sessions on administration of RAS. As a result, some providers lacked competency in administration of RAS. Additionally, job aids on RAS were not readily available, further contributing to low uptake of RAS at the health facilities.
    - Partial iCCM roll-out and exclusion of RAS in iCCM: iCCM is not being implemented nationally in Uganda. Even in areas where iCCM is in operation, CHWs are not currently provided with RAS. Failure to allow for administration of RAS by CHWs has limited the commodity's impact. As a result of limited availability at the community level, caregivers often go directly to HCIV and district hospitals for treatment.
2. Inadequate storage conditions: Storage conditions of RAS at HCII and HCIII were poor, with RAS products routinely exposed to temperatures above 30 degrees Celsius, leading to product deterioration and melting.
3. Lack of transportation options from primary to secondary facilities: Referrals are often not completed due to the absence of an affordable means of public transport.

Lessons learnt

[53] Severe malaria case management in Uganda. 2018

1. Demand generation and community sensitization for RAS are essential to ensure optimal uptake of the product. In addition, training and supervision will augment provider confidence and adherence to standard treatment protocols to allow for realization of the impact of RAS on U5 children.
2. Supervision efforts and enforcement of the use of 100mg QA brands will also help flush out non-QA RAS (currently in the Uganda supply chain) from previous procurements.
3. Storage conditions at peripheral facilities must be monitored to ensure storage of RAS product under manufacturer specified conditions and prevent product deterioration.
4. Ease of transportation from primary to secondary facilities is key to ensure successful completion of referrals.

Based on these findings, a number of common challenges emerged from the interviews across these countries: a) alignment of national severe malaria treatment guidelines on administration of RAS as a pre-referral intervention for children below the age of 6 with WHO guidelines; b) prevalence of expiry or stock-out of RAS products; c) deterioration of the RAS product due to product quality issues or exposure of the product to temperatures beyond 30 degrees Celsius; d) caregiver adherence to the health system referral pathway, ensuring that their children with severe malaria are first seen by CHWs or health centers who can administer RAS and; e) completion of referrals from the community or health center to the referral facility post administration of RAS. Table 2 provides a summary of these challenges. Despite these challenges though, there are great examples of where these challenges have been (partially) addressed; developing strong referral systems (i.e., Senegal), providing affordable modes of transport (i.e., Ghana, Senegal) or the incorporation of RAS into ICCM structures (i.e., Malawi)- illustrating that if well planned and executed, RAS can successfully be introduced and scaled.

Table 2: Summary of challenges identified in stakeholder interviews from multiple countries

Challenge		**Country**					
		DRC	**Ethiopia**	**Ghana**	**Malawi**	**Senegal**	**Uganda**
a)	National treatment guidelines not aligned with current WHO guidelines			x	x		x
b)	Expiry or stock-outs of RAS product	x	x			x	
c)	Reports of Product deterioration		x		x		x
d)	Care givers skip pre-referral intervention		x		x		
e)	Referrals not completed	x			x		

8. Recommendations

The landscaping assessment conducted here identified a number of challenges across countries that would need to be addressed to ensure safety, effectiveness, and efficient scale-up of RAS. To help address these challenges, we propose the following recommendations and considerations:

1. **Policy**: As countries introduce or look to scale up the use of RAS as a pre-referral intervention for severe malaria, they should take the opportunity to revise malaria treatment guidelines to align with WHO recommendations. Only slightly over half of countries known to have RAS in their guidelines have aligned with the most current WHO recommendations to date.

2. **Quantification**: Quantification of RAS has historically been weak, with product expiries or stock-outs observed due to inaccurate quantification. Because RAS products come with a limited shelf life, efforts

to promote accuracy of forecasts are essential, and must take into account the strength of the supply chain system as well as shelf life and temperature stability of the product.

3. **Product registration, procurement and distribution:** With the recent pre-qualification of the Cipla and Strides' 100mg RAS product, countries should select one of these products and avoid products of lower quality. Countries should explore a re-supply frequency of 1-3 months, and ensure that RAS products are not exposed to temperatures over 30 degrees Celsius. Furthermore, accurate demand forecasting, proper storage training and re-supplies in alignment with working iCCM re-supplies will minimize waste, stock outs and expiries.

4. **Temperature considerations**: Manufacturers state that Cipla and Strides RAS products cannot be stored or have temperature excursions over 30 degrees Celsius. It is important that supply chain agents are made aware of temperature requirements for RAS. At the community level, CHWs should also be made aware of temperature requirements. If products have melted or if there are otherwise visible signs of deterioration, the products should not be used but rather disposed of appropriately and safely. Post market surveillance should be in place to allow health workers to detect and report any faulty products.

5. **Training and supervision**: Effective RAS administration requires training to ensure health workers at numerous levels are not only aware of dosing requirements but are confident administrating RAS. Training and supervision at health post and community levels where RAS is administered have been found to be lacking. To avoid a situation in which health workers do not administer RAS because they are not well trained or are uncomfortable administering the suppository, it is critical that health workers receive ongoing training and mentorship, and are subject to regular supervision. When countries are developing iCCM or other community level trainings, RAS should be integrated into foundational trainings and not rolled out in isolation.

6. **Completion of referrals**: In settings where the community is far from the nearest referral facility, completion of referrals with treatment using Inj Art and a full course of ACTs after administration of RAS is complicated by absence and unaffordability of transportation, or lack of requisite treatment at the referral facilities. The ultimate effectiveness of RAS as a component of the complete severe malaria treatment process may depend upon whether affordable transportation is accessible to patients needing to move quickly between community and health facility. Referral facilities must also have the necessary Inj Art and ACTs to ensure the patient completes their severe malaria treatment and referral to achieve a complete cure and reduce the spread of resistance.

7. **Community engagement**: Care seekers often skip consultation at community or health post levels in favor of going directly to referral facilities, particularly when they identify that their children have severe febrile illness. When referral facilities are hours or days away, receiving RAS at community level first will save lives. Community engagement and education on severe malaria case management will help to encourage visits to health workers at the community level to receive RAS before commencing travel to a secondary facility.

8. Conclusion

Available evidence supports the efficacy of RAS as a life-saving intervention for children with severe malaria in remote settings. With the availability of quality-assured 100mg RAS products from Cipla and Strides, countries have the opportunity to introduce or scale-up RAS use at the community level. At the same time, there is a need for operational evidence to inform how such a scale-up can be conducted safely and effectively under real-world

conditions. Experience from countries with a history of RAS use indicates that good planning and well-functioning health systems play a key role in ensuring that RAS has its intended effect. Along with training and equipping health workers across numerous levels, efforts to sensitize communities, integrating RAS into iCCM, strengthening referral systems, ensuring high quality care at referral facilities, and robustly quantifying and distributing the product are necessary for a successful scale up of RAS. While RAS has the potential to save lives across high endemic Africa, maximizing its potential contribution requires careful attention to the myriad of components across the severe malaria treatment continuum of care.

9. Annex

1. RAS procurements by African countries (2007-2018)

Table 3: UNICEF, PMI, GPRM and MSF procurement aggregated by country, as reported to GPRM, PMI, UNICEF and MSF.

Country	Dosage	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Angola	100 mg									221862		**221,862**
Benin	50mg	270,000										**270,000**
Burkina Faso	50mg										40,002	**40,002**
Central African Republic	50mg						16,668			20,160		**36,828**
Chad	200mg						89,600					**89,600**
Democratic Republic of the Congo	50mg					5,133	125,346		132,696	37,236	18,618	**319,029**
	100mg									175,002	502,202	**677,204**
	200mg		393			6,273	967,326	37,189				**1,011,181**
Ethiopia	100 mg										90,000	
Eritrea	100 mg									4,560		**4,560**
Ghana	50mg		336,000			200,004	43,284			5,136		**584,424**
	100mg									28,044		**28,044**
	200mg					150,000				51,720		**201,720**
Guinea	50mg							120,000			48,000	**168,000**
	200mg							60,000			24,000	**84,000**
Guinea-Bissau	100mg									2,000	4,000	**6,000**
Kenya	100mg										494,550	**494,550**
Liberia	50mg						60,280					**60,280**
	200mg						81,751					**81,751**
Madagascar	100mg										60,000	**60,000**
Malawi	50mg					8,400		110,904			17,088	**136,392**
	100mg			-							9,000	**9,000**

Country	Dosage	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
	200mg			-								-
Mali	50mg	10,632	21,252		9,000							**40,884**
	100 mg									14,400		**14,400**
	200mg	13,704	27,408									**41,112**
Mauritania	200mg					750						**750**
Mozambique	50mg				34,852							**34,852**
	200mg				34,255							**34,255**
Niger	50 mg										8,640	**8,640**
	100 mg										155,400	**155,400**
Nigeria	100 mg										62,000	**62,000**
Senegal	50mg					36,000	36,000	39,600		91,680	45,840	**249,120**
	100mg						37,236					**37,236**
	200mg					28,680	36,000	61,200		138,000	69,000	**332,880**
Sierra Leone	50mg		6,941			936	1,190					**9,067**
Somalia	50mg				300							**300**
South Sudan	100 mg										60,000	**60,000**
Sudan	50mg	3,083										**3,083**
	200mg	3,197										**3,197**
Uganda	50mg		55,679		9,114	7,241					62,000	**134,034**
Zambia	100 mg									6,000		**6,000**
Zimbabwe	50mg						64,800			17,280		**82,080**
	200mg						97,200		83,880			**181,080**
Grand Total		**300,616**	**447,673**	**-**	**87,521**	**443,417**	**1,656,681**	**428,893**	**216,576**	**813,080**	**1,770,340**	**6,074,797**

Table 4: 50mg, 100mg, and 200mg Rectal Artesunate procurement volumes by funding source, according to data reported in the GPRM, UNICEF and PMI.

Category	Strength	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
GPRM	200 mg		36,120	77,028			4,998	102,204	414,660	49,500	28,320		
	100 mg												766,710
	50 mg	594,000	43,410	200,448	230,400	660		700,158	136,488	39,012	360		
PMI	200 mg			6,852	13,704			89,340	365,400	60,600	27,960	94,860	93,000
	100 mg											94,830	489,402
	50 mg			140,316	178,626			122,202	114,042	135,252	66,348	75,666	178,188
UNICEF	200 mg			19,182	2,358		205,530	42,138	167,448	7,890			
	100 mg												250,000
	50 mg			18,498	375,720		319,596	79,860	68,904				

2. Country scoring and selection methods

To select countries for an in person visit ('phase 2'), we created eight weighted criteria to score, compare, and rank the countries:

1. Endemicity (Malaria incidence 2015)
2. Malaria burden (Malaria deaths 2015)
3. RAS in guidelines (Y/N)
4. Alignment of guidelines to WHO recommendations (Y/N)
5. Previous and current procurement and/or use of RAS (Y/N)
6. Current procurement volume ordered (as of 2017 – Y/N)
7. Security (2017)
8. The presence of a CHAI office (Y/N)

Once information had been gathered on all these criteria for the 56 countries, they were indexed within each category. Each criterion was given a weight based on relative importance out of a score of 100. (See table below). The adjusted indexes were then combined into a composite score and the countries were ranked based on this score. This scoring system was shared with the WHO, UNICEF and PMI for feedback and adjusted as the landscaping progressed. For example, the weight for malaria burden increased to prioritize countries with high numbers of malaria deaths based on feedback from the WHO. Additional considerations for country selections identified during the review included the existence of community health workers (CHWs) who currently use RAS within an integrated community case management (iCCM) framework. Because this information was not available in a standardized format, it was not included as a quantitative criterion but was used to identify visited countries.

Table 5: Country evaluation criteria and corresponding weights

Index	Endemicity (Incidence)	Malaria burden	RAS guidelines	Correct guidelines	Previous and current procurement/use	Current procurement volume	Security	CHAI office	Total
Weighting	7.0	18.0	15.0	15.0	15.0	12.0	9.0	9.0	100.0

Table 6: Top 10 countries for RAS use based on weighted criteria (not including the three CARAMAL project countries DRC, Nigeria and Uganda)

Rank	Country	Prioritized for visit	Status
1	Mozambique	Y	Phone interviews conducted, which revealed very limited country experience with RAS use
2	Liberia	N	-
3	Malawi	Y	Completed
4	Senegal	Y	Completed
5	Benin	N	-
6	Ethiopia	Y	Completed
7	Sierra Leone	Y	Interviews conducted by CHAI Sierra Leone staff which revealed very limited country experience with RAS use
8	Chad	N	-
9	Mali	N	-
10	Ghana	Y	Completed

3. Rectal Artesunate (RAS) Questionnaire

I. Policy and guidance

1. When was rectal artesunate included in the country's treatment guidelines?
2. Has the policy been modified in any way since then?
3. Are the guidelines in-line with WHOs recommendations for use only in pre-referral of U6 severe malaria cases? (Refer to existing landscaping)
    a. If not, why?
    b. Are there plans to correct it?
4. Are there guidelines for use of rectal artesunate outside of pre-referral severe malaria treatment?
5. Is rectal artesunate also on the essential medicines list? (Refer to existing landscaping)

II. Use and Case management

1. Is rectal artesunate used for anything other treatments outside the country's guidelines of specified use?
2. Is RAS currently being used nationwide? Or just in a few select areas?
    a. If it is only being used in select areas, what are these areas and how were they chosen?
    b. Is there a plan for scale up and if so what is it?
3. Has there been a successful use of RAS based on existing policy?
    a. If yes, why was it successful? What strategies were key?
    b. If not, why was it unsuccessful? What barriers/challenges did you face? (Probe use in uncomplicated malaria)
    c. What would you recommend other countries consider or do to achieve success and/or avoid the pitfalls your country made?
4. Did you have any partner support for RAS introduction and scale up?
    a. What partners and what kind of support did they offer?
    b. For how long?
5. What are the opportunities and challenges on management of children presenting with signs of severe malaria at the community level?
6. Have you observed any improvements in severe malaria case management?

III. Formulation, procurement and supply chain

1. What are the steps taken to procure RAS?
2. What brand(s) and formulation(s) of RAS (and Inj. Art) are registered in the country?
3. What brand(s) and formulation(s) of RAS (and Inj. Art) does the country/partners buy?
4. CIPLA and Strides have received ERP approval for their rectal artesunate. If these are not currently the brands procured by the country, is it likely that the country could switch to these brands?
    a. If no, why not? If yes, when do they plan to switch and to which brand?
5. Can we validate our volume numbers? (Refer to volume figures in landscape)
6. Who is funding and procuring RAS?
    a. Please define in quantities or percentages (refer to landscaping)
7. When RAS (and Inj. Art) is procured, how is it stored and distributed?
    a. What is the process of getting it from the central store to the community level?

b. Is it push or pull system?
c. What is the resupply frequency at each level?
d. What are the ambient temperatures along the supply chain and at the community level like?

8. What are the future sources of funding for Severe malaria treatment
    a. RAS
    b. Inj. Art

IV. Health systems, programs and capacity

1. At what level of the health system is severe malaria treated?
    a. If a patient seeks care for severe malaria at a lower level facility, how does the facility manage them? (Prompt about community level health workers if not mentioned)
    b. Do you have a referral system from the lower levels of care? If so, please describe it.
    c. What are the challenges with referral systems?
2. How is malaria data reported from the levels of care mentioned above?
    a. Do you have mobile reporting systems in place?
    b. Is the country using DHIS2?
    c. Do you track severe malaria referrals?
3. Which health workers are trained on the use of rectal artesunate?
4. Do you have an ICCM program in place?
    a. If yes, since when?
    b. Is it national or in some select areas?
    c. If in select areas, please name them
    d. Is there a partner supporting the program? If so, who, when and where?
    e. Who manages the health workers within the ICCM program?
    f. Is the use of RAS integrated in the ICCM program?
5. What are the opportunities and/or challenges with handling and dispensing RAS?
    a. Community health workers
    b. Primary care facilities
    c. Referral facilities
6. What efforts (across all levels of care) have been made to improve severe malaria case management?
    a. Were any such efforts due to the introduction of RAS?

4. RAS procurement and guidelines summary

Red: Non-alignment with WHO guidelines (24)
Amber: Unknown/unavailable guidelines (18)
Green: Alignment with RAS guidelines (14)

Table 7: RAS Country alignment with WHO RAS guidelines, procurement and guidelines summary, as of November 2018

s/n	Country	Age of RAS use	History of RAS procurement	Planned procurement (in 2018)	CHWs exist?	ICCM program exists?	CHW that uses RAS	RAS in ICCM	More than 1 dose	Use in uncomplicated malaria
1	**Algeria**		N							
2	**Angola**	Up to Adulthood	Y		Y	Y			N	N
3	**Benin**	U5	Y		Y	Y			Y	N
4	**Botswana**	U6	N		Y	N			N	N
5	**Burkina Faso**		N	Y	Y	Y				
6	**Burundi**		Y		Y	Y				
7	**Cameroon**		Y		Y	Y				
8	**Cape Verde**		N							
9	**Central African Republic**		Y			Y				
10	**Chad**	U5	Y						N	N
11	**Comoros**	Not clear	N		Y	N			-	-
12	**Congo, Democratic Republic of the**	U5	Y	Y	Y				N	N
13	**Congo, Republic of the**		N		Y	Y				
14	**Cote d'Ivoire**	U5	Y		Y	Y			N	N
15	**Djibouti**		N		Y	Y				
16	**Egypt**		N		Y	N				

s/n	Country	Age of RAS use	History of RAS procurement	Planned procurement (in 2018)	CHWs exist?	ICCM program exists?	CHW that uses RAS	RAS in ICCM	More than 1 dose	Use in uncomplicated malaria
17	**Equatorial Guinea**	U5	Y		Y	N			-	-
18	**Eritrea**		N		Y	Y				
19	**Ethiopia**	U6	Y		Y	Y	Y	Y	N	N
20	**Gabon**		N			N				
21	**Gambia, The**	U5	N		Y	N			-	-
22	**Ghana**	Up to Adulthood	Y		Y	Y	Y		-	-
23	**Guinea**	Up to Adulthood	Y		Y	Y			-	-
24	**Guinea-Bissau**		Y		Y	Y				
25	**Kenya**	U6	Y	Y	Y	Y			N	N
26	**Lesotho**		N							
27	**Liberia**	U6	Y		Y	Y			N	N
28	**Libya**		N							
29	**Madagascar**	U5	Y	Y	Y	Y			N	N
30	**Malawi**	U6	Y		Y	Y	Y		N	N
31	**Mali**	Up to Adulthood	Y		Y	Y			N	N
32	**Mauritania**		Y		Y	Y				
33	**Mauritius**		N							
34	**Mayotte**		N							
35	**Morocco**		N			N				
36	**Mozambique**	U6	Y		Y	Y	Y		Y	N
37	**Namibia**		N		Y	N				
38	**Niger**		Y		Y	Y				

s/n	Country	Age of RAS use	History of RAS procurement	Planned procurement (in 2018)	CHWs exist?	ICCM program exists?	CHW that uses RAS	RAS in ICCM	More than 1 dose	Use in uncomplicated malaria
39	**Nigeria**	Up to Adulthood	Y		Y	Y			N	N
40	**Republic Arab Sarawahi Democratic**		N			N				
41	**Rwanda**		N		Y	Y				
42	**Sao Tome and Principe**		N							
43	**Senegal**	U6	Y		Y	Y	Y		N	N
44	**Seychelles**		N							
45	**Sierra Leone**	Up to Adulthood	Y		Y	Y			N	N
46	**Somalia**		Y			N			N	N
47	**South Africa**		N		Y	N				
48	**South Sudan**	Up to Adulthood	Y						N	N
49	**Sudan**	Not clear	Y		Y	Y			Y	N
50	**Swaziland**		N		Y	N				
51	**Tanzania**	Up to Adulthood	Y		Y	N			N	N
52	**Togo**		N		Y	Y				
53	**Tunisia**		N			N				
54	**Uganda**	Up to Adulthood	Y		Y	Y			N	N
55	**Zambia**	Up to Adulthood	N		Y	Y			N	N
56	**Zimbabwe**	Up to Adulthood	Y		Y	Y			N	N

5. List of stakeholders consulted

Table 8: List of stakeholders consulted

#	Name	Affiliation
1	Dr. Doudou Sene	PNLP Senegal
2	Dr. Seynabou Gaye	PNLP Senegal
3	Dr. Ibrahima Diallo	PNLP Senegal
4	Dr. Ndella Diakhate	Intrahealth Senegal
5	Dr. Mame Diouf	PMI Senegal
6	Dr. El Hadji Yankhoba Dial	Intrahealth Senegal
7	Dr. Alioune Gueye	PNLP Senegal
8	Dr. Mady Ba	WHO Senegal
9	Dr. Ndella Diakhate	WHO Senegal
14	Dr. Katherine Sturm-Ramirez	PMI Senegal
15	Dr. Awa Diallo Bathily	UNICEF Senegal
16	Mr. Newton Temani	MOH iCCM Malawi
17	Mr. Gomezgani Jenda	Save the Children - Malawi
18	Mr. Texas Zamasiya	UNICEF Malawi
20	Ms. Elizabeth Mkandawire	NMCP - Malawi
21	Mr. John Sande	NMCP - Malawi
22	Dr. Wilfred Dodoma	WHO - Malawi
23	Mrs. Hiwot Teka	PMI - Ethiopia
24	Dr. Dereje Mulneh	UNICEF - Ethiopia
25	Mrs. Hiwot Solomon	NMCP Ethiopia
26	Dr. Sami Tewfik	JSI - Ethiopia
27	Dr. Agonafer Tekalegn	Malaria Consortium - Ethiopia
28	Ato Azemeraw	PFSA Ethiopia
29	Regis Magauzi	PMI - Zimbabwe
30	Christie Billingsley	PMI - Zimbabwe
31	Peter Troell	PMI - Zimbabwe
32	Dr. Melba Filimina Gomes	WHO - TDR
33	Dr. Piero Luigi Olliare	WHO - TDR
34	Prof. Christian Burri	Swiss TPH
35	Prof. Christian Lengeler	Swiss TPH
36	Dr. Aita Signorell	Swiss TPH
37	Dr. Manuel Hetzel	Swiss TPH
38	Dr. Silvia Schwarte	WHO
39	Dr. Salim Sadruddin	WHO
40	Dr. Peter Ehizibue Olumese	WHO
41	Mr. Pierre Hugo	MMV
53	Ms. Kim van der Weijde	MMV
54	Mr. Alex Ogwal	CHAI
55	Ms. Carine Olinga	CHAI

56	Dr. Martin de Smet	MSF
57	Dr. Eric Halsey	PMI
58	Ms. Roopal Patel	GFATM
60	Dr. Meera Venkatesan	PMI HQ
61	Ms. Valentina Buj	UNICEF
62	Ms. Farhana Zuberi	UNICEF
63	Mr. James Frimpong	NMCP Ghana
64	Dr. Jon Eric Tongren	PMI Ghana
65	Dr. Sixte Zigirumugabe	PMI Ghana
66	Mr. Laud Reginald Tetteh Baddoo	USAID Global Health Supply Chain Program, Ghana
67	Mr. Deogratius Kimera	USAID Global Health Supply Chain Program, Ghana
68	Dr. Felicia Owusu-Antwi	WHO Ghana
69	Dr. Daniel Yayemain	UNICEF Ghana
70	Dr. Kezia Malm	NMCP Ghana
71	Dr. Yanti Pasaribu	UNICEF Supply Division
72	Dr. Joyce Bakka	UNICEF Supply Division
73	Dr. Dennis Rubahika	NMCP Uganda
74	Mr. Mathias Kasule	NMCP Uganda
75	Dr. Eric Sompwe	PNLP DRC
76	Dr Joris Likwela	PNLP DRC