End-of-Grant Evaluation Report

Community Access to Rectal Artesunate for Malaria (CARAMAL) Project and Output 3 of the Supply Side Grant

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List of Abbreviations

BMGF	Bill & Melinda Gates Foundation
CARAMAL	Community Access to Rectal Artesunate for Malaria
CCM	Country Coordinating Mechanism
CHAI	Clinton Health Access Initiative
CHW	Community Health Worker
DAC	Development Assistance Criteria
DHS	Demographic and Health Survey
DRC	Democratic Republic of Congo
HeRAMS	Health Resources and Mapping System
iCCM	Integrated Community Case Management
KIIs	Key Informant Interviews
KPIs	Key Performance Indicators
LMCU	Logistics Management Coordination Unit
LMICs	Low- and Middle-Income Countries
MMV	Medicines Malaria Venture
NMCP	National Malaria Control Program
NMEP	National Malaria Elimination Program
OECD	Organisation for Economic Co-operation and Development
PMI	President Malaria Initiative
PNLP	Programme National de Lutte contre le Paludisme
PQP	Pre-Qualification Program/Process
PR	Principal Recipient
QA	Quality Assured
RAS	Rectal Artesunate
RHITES	Regional Health Integration to Enhance Services Project
ROI	Return on Investment
SANRU	Santé Rurale
SR	Sub Recipient
Swiss TPH	Swiss Tropical & Public Health Institute
TWG	Technical Working Group

Executive Summary

BroadImpact was appointed by Unitaid to conduct the End-of-Grant Evaluation of the Community Access to Rectal Artesunate for Malaria (CARAMAL) project and Output 3 of the Supply Side grant. The evaluation was conducted between January and April 2021.

Unitaid committed up to US$ 19 million to demonstrate the appropriate use of Pre-referral Rectal Artesunate (RAS) in real life settings through the CARAMAL project. The project was designed to inform operational strategies for the introduction and scale-up of RAS in diverse settings including community and primary health care settings. It was implemented by a consortium comprising Clinton Health Access Initiative (CHAI)-lead grantee, UNICEF, and Swiss Tropical and Public Health Institute (Swiss TPH), in 3 focus countries; Nigeria, The Democratic Republic of the Congo (DRC) and Uganda. Swiss TPH also signed contracts with research partners: University of Kinshasa in DRC, Akena Associates in Nigeria and Makerere University in Uganda. The project aimed to increase access to Quality Assured (QA) RAS as part of strengthened severe malaria case management systems, with a goal to reduce malaria mortality in children under 5 globally. The project started in August 2017 and ran up till April 2021. Medicines for Malaria Venture (MMV) was also funded by Unitaid to implement the Supply Side grant and work alongside the CARAMAL project to improve global supply of QA RAS by providing technical support to manufacturers for product prequalification through the WHO Pre-Qualification Program (PQP). The MMV Supply Side grant was implemented from September 2017 to December 2020 and has now been extended till December 2022 to attain other deliverables unrelated to RAS. WHO was also funded through an enabler agreement to support evidence generation to facilitate delivery of a normative operational guideline and advocate for broader scale-up across project and non-project countries.

Throughout the report we refer to the CHAI led CARAMAL project as the ***"CARAMAL project"*** and the MMV Supply Side Grant as the ***"Supply Side grant".*** Where we describe the joint efforts of both projects, we refer to them as "***the projects".***

The evaluation aimed to assess the overall performance of the projects across the following Organisation for Economic Co-operation and Development (OECD), Development Assistance Criteria (DAC)**:** relevance, coherence, effectiveness, efficiency, impact and sustainability as well as the identification and synthesis of knowledge on good practices and lessons learned. The evaluation found the design of the projects to be very **relevant** and responsive to the current needs of targeted beneficiaries in malaria endemic countries, and malaria response stakeholders globally. The intervention contributes to addressing the persistently high malaria burden and mortality rates, it provides an additional strategy for severe malaria management among children under 5 at community level and informs the development of the much-needed WHO operational guidelines for an underutilized product that countries were already rolling out.

The CARAMAL project was inherently **coherent**, as it was designed to fit within the health system and leverage existing structures especially the Integrated Community Case Management (iCCM) systems in project countries. The project was almost seamlessly integrated within iCCM and other related health systems structures during implementation. The Supply Side grant was also coherent as it fit very well with the CARAMAL project's commodity prequalification, registration and availability needs; it also created valuable and productive connections between the CARAMAL project, manufacturers and the WHO PQP.

The CARAMAL project was **moderately effective** with solid performance across most of its results areas. The Supply Side grant also successfully delivered its third output, and together with the CARAMAL project increased access to QA RAS through the introduction of the first **quality** assured

100mg RAS products through the WHO prequalification, which are now globally **available** through two manufacturers, Cipla and Strides. The projects facilitated increased **demand, adoption** and scale up efforts through co-creation of Behaviour Change Communication (BCC) Interventions with in-country stakeholders; leveraging existing IEC (Information Education and Communication) tools previously developed by MMV; and providing technical support to non-project countries to inform guideline alignments and strategic plans. Optimizing the efficiency of distribution systems to ensure **supply and delivery** of commodities to those in need in a reliable and timely way was one of the most critical supply chain processes the CARAMAL project encountered and addressed; this was evidenced by minimal levels of stockouts of QA RAS ranging from 1%-14%, well below the projected target of 20%. The CARAMAL project ensured consistent supply by the integration of QA RAS into national drug supply systems including the existing iCCM supply systems, other donor supported processes as well as providing additional support where needed to cushion emerging supply chain gaps. Overall, solid progress has been made against the three target Unitaid's market access barriers (quality, demand & adoption and supply & delivery). The projects were also very effective in positioning themselves to catalyse the global market, by working strategically with manufacturers to influence RAS price setting and leveraging other donor funds for scale up. There has been an increase in RAS procurements in project and non-project countries, with 22 countries (19 in sub-Saharan Africa) procuring this commodity in 2020 as compared to a baseline of only 8 in 2018. This could not have been achieved without the presence of these Quality Assured products.

In terms of **efficiency,** the CARAMAL project had a lower budget consumption in its first year due to protracted ethics review processes and late receipt of its first-year funding, however the project increased its budget consumption annually, in tandem with the scale up of project activities and was proactive in adjusting and realigning budgets each year. The funding split across outputs was optimal and was sufficient to complete activities per the program design. The factors utilized to achieve value for money included integrating the intervention within existing health systems structures, and leveraging other partners and donor funded activities in project locations. The project team also made concerted efforts to ensure that national and sub-national level authorities within the project countries were actively engaged throughout the life of the project. The consortium arrangements worked quite well, with strong collaboration and transparency across partners.

The **impact** of the RAS intervention could not be accurately measured in terms of Case Fatality Ratio (CFR) comparisons based on its original pre-post design as this was limited by a myriad of contextual challenges that made the project implementation phase very different from its baseline. While it was clear that such a before-after evaluation was sub-optimal, there was really no better design available in practice. Contextual challenges that affected the comparability of the pre- and post- intervention periods resulted from the fact that the RAS intervention was integrated into real-world existing health systems, which allowed for inherent weaknesses of the systems such as inadequate referral mechanisms and suboptimal supply chains. These two challenges were out of the CARAMAL project's implementation scope to address per project design, but substantially limited the effectiveness of the intervention especially with respect to reducing CFR, as many children did not complete treatment at a health facility after receiving RAS in the community. The CARAMAL project also had a very ambitious project timeline of reducing mortality in about 18 months of implementation.

Despite the challenges, the potential impact of the projects was estimated through modelling by the evaluation team. The evaluator's modelled estimates show that the projects could contribute to 47,152 [0 – 68,381] lives saved and 2.7m [0 – 4.0m] DALYs averted from 2020-2026 across Africa. The projects will confer an incremental cost of US$57m [49m, 63m] to the health system, with an average cost of US$34 [32,37] per child receiving RAS. The public health impact of RAS, however, will result in positive productivity gains/net savings, with a very high Return on Investment (ROI). The impact value ranges indicate the possibility of not achieving impact with the zero value and the negative net cost

representing scenarios where follow up services post-RAS implementation are not available, resulting in increased costs to the health system without any commensurate public health benefit. Beyond the potential number of lives saved, the projects' beneficiaries were primarily vulnerable populations, including children under 5 who are the most susceptible to malaria, communities in high malaria endemic areas with limited access to health care, and governments of Low- and Middle-Income Countries (LMICs) with significant health systems gaps; depicting its heavy focus on equity and serving underserved populations.

The CARAMAL project is poised to be **sustainable,** with a very robust sustainability plan developed at inception; a donor landscaping steering committee that created greater knowledge around the historical and future trends of RAS orders, procurement and uptake; regular and continued engagement with in-country Technical Working Groups (TWGs), WHO and global audiences to disseminate preliminary findings and share lessons learnt; and technical support to project and non-project countries for strategic plan and guideline revisions, inclusion of RAS into essential medicines lists and iCCM structures; as well as into requests to other donors such as the President's Malaria Initiative (PMI) and Global Fund (GF). The immediate commitments for RAS procurements in the 3 project countries are heavily donor dependent and will definitely ensure short term sustenance, but in the long term, financial resources will need to be identified to enable further expansion and sustainability. Achieving the full potential of the RAS intervention goes beyond securing funding for ongoing procurement, there must be commensurate support for addressing the health systems strengthening constraints earlier described.

Recommendations to National Malaria Control Programs (NMCPs) and Ministries of Health include implementing a systems rollout approach for RAS by; determining and incorporating supportive interventions that address the most critical health systems gaps per country specific assessment; jointly procuring and monitoring case management commodities (RAS, Rapid Diagnostic Tests (RDTs), Injectable Artesunate (Inj AS), Artemisinin Combination Therapies (ACTs)); development of PSM guidelines for RAS with clear processes for forecasting, distribution to remote CHWs, commodity exchange and temperature regulation options; mobilizing resources to support systems strengthening; and ongoing documentation of lessons learnt and best practices for program improvement. For countries with a large population seeking care from the private sector, it is also important to establish or leverage national frameworks for private sector engagement. Future donor funded projects should support a larger case management program or iCCM program which includes RAS as opposed to implementing a standalone intervention focused on RAS. The upcoming WHO field implementation guide should include guidance on addressing the low referral completion, low follow up treatment rates and the resulting high monotherapy risk observed in the CARAMAL project. This may include specifications on how CHWs are networked with referral facilities and guidance on key messaging to address the RAS monotherapy risk. In designing similar projects, it would be important for Unitaid to ascertain the validity of project design assumptions including outcome and impact measures during project baseline assessments with room to adjust the project's Theory of Change, especially with critical foundational project elements as well as feasibility of proposed results. Alternative implementation approaches to consider are phased integration efforts with a longer timeframe to address the most critical health systems obstacles, or formalized partnerships with existing health systems strengthening projects. Scoping innovative opportunities that will enable referral pathways in LMICs will also be important, as referral systems are a very critical impediment to successful implementation of this project and many others in LMICs. Lastly evaluating different packages of supportive interventions or Health Systems Strengthening (HSS) conditions will be important when implementing similar interventions to RAS which leverage on a broader system.

1. Introduction

1.1 Background

Malaria is one of the leading causes of illness, death, and lost economic productivity in the world. An estimated 229 million malaria cases occurred globally in 2019, the majority of which occurred in sub-Saharan Africa. DRC, Nigeria, and Uganda collectively account for 42% of the global burden of malaria.[1] *Plasmodium falciparum* is the most implicated parasite in sub-Saharan Africa followed by *Plasmodium vivax.* Infants over 3 months of age in these malaria-endemic areas are more vulnerable to *Plasmodium falciparum* malaria, and are at an increased risk of rapid disease progression, severe malaria and death, especially as the immunity acquired from their mothers begins to wane. Malaria is preventable with the mass distribution and use of insecticide- treated nets. Together with prompt access to effective treatment with antimalarials, malaria mortality and morbidity rates can be significantly reduced. Mortality persists in areas where timely access to treatment is hindered and within vulnerable population groups such as children and pregnant women. There are limited numbers of infant formulation for most antimalarials with a potential result of inaccurate dosing of infants, furthermore infants tend to deteriorate quickly so require a low threshold for parenteral treatment. Therefore, for severe cases where it isn't possible to access parenteral treatment, 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 Inj AS and a course of ACTs. The single dose of pre-referral RAS has been found to reduce the risk of death among infants with severe malaria.[2]

1.2 Programme Description

Pre-referral rectal artesunate had been introduced into national treatment guidelines of 16 African countries by 2016; with variations that did not align with WHO recommendations, limited operational guidance and probably the most critical gap, the absence of a commercially available Quality Assured (QA) product. The only study conducted at the time showed both a reduction in malaria related mortality among children under 6 and an increase in mortality among children over 6 years.[3]

The Community Access to Rectal Artesunate for Malaria (CARAMAL) project is a USD$ 19 million grant funded by Unitaid to inform operational strategies for the introduction and scale up of RAS in diverse settings including community and primary health care settings. The project primarily focuses on 3 countries (Nigeria, DRC and Uganda). CARAMAL is implemented by a consortium comprising CHAI as lead grantee, UNICEF, and Swiss TPH. Swiss TPH also signed contracts with research partners in each of the three countries: University of Kinshasa in DRC, Akena Associates in Nigeria and Makerere University in Uganda. The project outcome is increased access to QA RAS as part of strengthened severe malaria case management systems, and its goal is to contribute to reducing malaria mortality in children globally. The project started in August 2017 and ran up till April 2021. MMV was also funded by Unitaid to implement the Supply Side Grant and work alongside the CARAMAL project to improve global supply of QA RAS for management of severe malaria after the WHO PQP approval. The MMV Supply Side Grant was implemented from September 2017 to December 2020 and has now been extended till December 2022 for other activities unrelated to RAS. WHO was also funded through an enabler agreement to support evidence generation to facilitate delivery of a normative guideline and advocate for broader scale up across non-project countries.

[1] World Malaria Report 2019

[2] Severe Malaria in infants https://www.severemalaria.org/severe-malaria/groups-at-risk/severe-malaria-in-infants Accessed (15-02-2021)

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

1.3 Theory of Change

CARAMAL & SUPPLY SIDE (O.3) THEORY OF CHANGE

Problem

Public Health Need

- Malaria still claims over 400,000 deaths annually, most of which are children under 5 and pregnant women with limited access to health facilities.
- The target beneficiary countries DRC, Nigeria, and Uganda, have a high burden of malaria and account for 42% of cases and 39% of deaths globally.

Access Barriers

1. **Quality:** No WHO PQP QA product, countries procuring non-quality assured RAS products
2. **Supply & Delivery:** Gaps in understanding operational feasibility within existing health systems, challenges with <30ºC storage requirements and 4-6 month commodity exchanges, distribution to CHWs in hard to reach areas
3. **Demand & Adoption:** Underutilized intervention (available for 15yrs), misalignment of country guidelines with WHO, no WHO field implementation guidance

Conceptual Pathway

Input	Outputs	Outcomes	Impact
❑ UNITAID funding - $19 mil for 3 years ❑ Supply side interventions to create access to quality assured products ❑ Country's iCCM and health system as implementation platforms	❖ **MMV Supply Side Output 3**: Improved QA RAS global supply for Mgt at Severe malaria ❖ **CARAMAL Output 1:** QA RAS available in country ❖ **CARAMAL Output 2:** RAS introduced as pre-referral treatment ❖ **CARAMAL Output 3:** Evidence generated & shared on use of RAS ❖ **CARAMAL Output 4:** Transition of evidence based & step wise scale-up	Increase access to QA RAS as part of strengthen malaria case management systems ✓ **Quality:** RAS is quality-assured through WHO-PQP and commercially available for rapid introduction ✓ **Supply & Delivery**: Supply chain systems effectively deliver adequate quantities of viable RAS to end users in a reliable and timely way. ✓ **Demand & Adoption**: Evidence of effectiveness of RAS in real-life settings. Countries, programs, and end users adopt RAS, RAS is integrated within iCCM with linkages to referral facilities	Aligned to Unitaid strategic KPIs and public health need above **Quantitative**: ✓ KPI 4.1 Reduction in CFR among severe malaria cases, # of lives saved ✓ KPI 4.2 Financial savings & health systems efficiencies ✓ KPI 4.3 Return on investment **Quantitative:** ✓ KPI 5.1 & 5.2 Equity impact, other strategic benefits/ positive externalities

Key Risks/ Assumptions

Risks

Strategic Risks: Severe disease rates and/or treatment seeking for severe disease at the community could be substantially lower than expected, significantly affecting evidence generation

Implementation Risks: Weak iCCM Platforms and referral systems to integrate the intervention;

Sustainability/Scalability Risks: Substantial supportive interventions are required to ensure that QA RAS is appropriately used.

Assumptions

- There is strong political willingness among target countries to adopt the intervention
- iCCM platforms and referral systems are well functioning and referral facilities are stocked severe malaria management commodities
- The evidence generated supports the notion that QA RAS can safely & cost-effectively be scaled up globally in communities with strong CHW networks
- Non-project countries will be influenced by evidence generated by the project & willing to make guideline updates on that basis
- Donors will be willing to commit funds to scale-up of RAS & countries willing to prioritize this intervention to be included in donor requests
- COVID-19 disruptions are minimal

2 Purpose & Scope of the Evaluation

2.1 Purpose

The evaluation aims to assess the overall performance of the CARAMAL project & Supply Side grant across the following OECD DAC evaluation domains**: relevance, coherence, effectiveness, efficiency, impact and sustainability** as well as the identification and synthesis of knowledge on good practices and lessons learned across all program outputs for the CARAMAL project from August 2017 to April 2021 and output 3 of the Supply Grant from September 2017 to December 2020.

2.2 Objectives

Specifically, the evaluation objectives are:

1. **To assess the effectiveness of the implementation approach**
   - promoting appropriate use of QA RAS in project and non-project countries including policy revisions
2. **To assess the effectiveness in evidence generation and advocacy efforts especially in**
   - promoting donor support and
   - driving scale up in project and non-project countries
3. **To determine the extent to which the implementation has driven and catalysed the global market and supply in terms of volume and prices**
4. **To determine the overall impact of RAS with reference to Unitaid's Strategic KPI 4 & 5**
   - Evaluate the potential impact with respect to the (i) expected public health impact, (ii) expected economic impact, (iii) return on investment, (iv) equity impact and (v) strategic benefits and positive externalities.
   - As part of the indirect public health impact, develop estimates of potential impact of RAS rollout from 2020 to 2026.
5. **To assess grant performance against relevant Strategic KPIs, with a focus on the main critical access barriers:** (i) Quality (ii) Demand and Adoption and (iii) Supply and Delivery.

2.3 Project Countries

The evaluation covers the three implementation countries: Nigeria, Uganda and the Democratic Republic of Congo (DRC). It also reviewed scale up reports and data from other malaria endemic countries (non-project countries) to assess the catalytic effect of the project on scale up and impact. See below descriptions of the project sites in each of the project countries.

2.3.1 Nigeria

The project was implemented in Adamawa State located in the North Eastern part of Nigeria with an estimated population of 4.2 million according to the National Population Commission of Nigeria. The project study area covers 6,000 children under the age of six years selected from three LGAs, namely **Mayo Belwa, Fufore and Song**. Adamawa state remains a malaria high risk area especially for the vulnerable (children under the ages of 5 years and pregnant women). Healthcare services in Borno and Adamawa states have been severely disrupted by the ongoing crisis in the North East region of Nigeria. This has in turn resulted in increased morbidity and mortality from preventable diseases such as malaria. Reports from the WHO Health Resources and Mapping System (HeRAMS) in Adamawa indicate that 46% of the 1,120 health facilities in the state are fully or partially damaged due to on-going crises[4]. Malaria is hyper endemic throughout the semi-arid zone of Adamawa State. Adamawa and other States in the North East make up the Sahel in Nigeria, where peak transmission occurs during the middle to late rainy season. While studies on seasonality are limited in Nigeria, a study conducted in 2012, in the neighbouring Maiduguri town in Borno State indicated a mean prevalence

[4] https://www.afro.who.int/news/who-deploys-nearly-4000-volunteers-tackle-malaria-borno-and-adamawa-states (Accessed 15-02-2012)

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of 35.2%.[5] Monthly figures of malaria among in-patients in Adamawa State show seasonal fluctuations; low values characteristic of the dry season and high values in the rainy season. Accordingly, malaria related morbidity and mortality show seasonal trends with peaks in the wet season and a low level in the dry season. According to the World Health Organization, Nigeria bears the highest burden of malaria in the world.

2.3.2 Uganda

The project was implemented in **Apac, Oyam and Kole** districts which are located in the Lango sub-region of Northern Uganda with a combined population of 808,293 (per the 2014 census). These districts have similar climatic conditions with temperatures ranging between 16 and 32°C, relative humidity of 50–80% and two rainy seasons all of which promote malaria transmission. District-level data indicates that these districts experience two peaks of malaria transmission in tandem with the two rainy seasons per annum. The districts were part of the 10 districts that implemented Indoor Residual Spraying (IRS) in a bid to control the malaria epidemic in Northern Uganda and were also among the most affected during the 2015/2016 malaria upsurge which occurred following transition from IRS to Insecticide-treated bed nets (ITNs).[6] [7] In 2019, another upsurge of malaria cases was reported in the region with an increase in cases reported at both facility and community levels. The ministry of health attributed this to heavy and intermittent rains, ageing of nets, changes in behavioral patterns and influx of refugees.[8] The Lango sub-region has a malaria prevalence of 13%.[9]

2.3.3 Democratic Republic of Congo

The project was implemented in 3 health zones in DRC namely: **Kenge** health zone located in the Kwango Region, **Kingandu** and **Ipamu** both located in the Kwilu Region. In view of its proximity to the capital Kinshasa, and being the regional capital itself, Kenge is easily accessible after a three-hour drive. However, implementing in Kingandu and Ipamu pose serious challenges in view of their remoteness from the Kwilu region capital Kikwit and especially due to the poor road network during the rainy season. The project intervention districts are based in Western regions of the DRC which are relatively secure as opposed to the Eastern part of the country where there has been protracted intertribal, interethnic regional and civil conflict for decades. The insecurity levels from baseline and throughout implementation of the project have been relatively the same so the project results are not expected to be impacted differently by this. Accurate and reliable data on DRC malaria prevalence and mortality is scarce or not available. As is the case in other countries in sub-Saharan African countries, pregnant women and under 5 children bear the greatest burden of malaria infection. According to the World Health Organization, DRC bears the second highest burden of malaria in the world. A provincial stratification based on malaria parasite prevalence, places the Kwilu and Kwango regions under the meso endemic Equatorial and Tropical regions with a malaria parasite prevalence of 6 to 30%.[10]

[5] L.M Samdi, J.A Ajayi, S. Oguche, A. Ayanlade. 2012.Seasonal Variation of Malaria Parasite Density in Pediatric Population of North Eastern Nigeria. Global Journal of Health Science. Vol. 4, No. 2; March 2012.

[6] "Uganda - Malaria Operational Plan FY 2019 - President's Malaria ...." https://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy19/fy-2019-uganda-malaria-operational-plan.pdf?sfvrsn=3. Accessed 14 Feb. 2021.

[7] "Government undertakes Indoor Residual Spraying (IRS) in 10 ...." 21 Jul. 2016, https://reliefweb.int/report/uganda/government-undertakes-indoor-residual-spraying-irs-10-epidemic-districts-northern. Accessed 14 Feb. 2021.

[8] "PRESS RELEASE - Uganda Media Centre." 12 Aug. 2019, https://www.mediacentre.go.ug/sites/default/files/media/Press%20Release-%20Ministry%20of%20Health%20issues%20advisory%20on%20rise%20in%20Malaria%20cases.pdf. Accessed 14 Feb. 2021.

[9] Uganda Malaria Indicator Survey (2018-2019)

[10] DRC Demographic and Health Survey II 2013-2014.

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3 Methodology

The evaluation framework and methodology are based on Unitaid's evaluation framework, strategic Key Performance Indicators (KPIs) and scalability framework applicable to the CARAMAL project and Supply Side grant.

3.1 Evaluation Approach

The evaluation involved a rapid portfolio mapping for each country, followed by a mixed-methods approach that comprised site visits, qualitative interviews; desk reviews of existing project documents, reports and other publications to harness qualitative and quantitative data; and subsequently estimating the expected public health and economic impact of the program through modelling.

The evaluators also identified impactful human angle/interest stories that further amplify the projects outcomes and lessons. These can be used as potential advocacy tools for ongoing engagement with key stakeholders.

The data collection processes were interactive and participatory, with a goal to ensure the collection of an in-depth, credible and accurate picture of the projects as documented through the life of the projects and as perceived by key stakeholders.

3.2 Sampling & Sample Size

The sampling for the qualitative interviews was purposive, but took into consideration representativeness of all key stakeholders in each of the countries and globally, variation by including a range of stakeholders with different dimensions of interest and optimizing cost by limiting the number of operational areas from which respondents were selected.

A total of 92 participants were interviewed, either one on one or in groups, these included 21 participants in DRC, 25 in Nigeria, 16 in Uganda and 30 global respondents. Respondents were Lead grantees (CHAI & MMV), Consortium partners (Swiss TPH &UNICEF), Manufacturers (Tridem and Strides), Global Fund, President Malaria Initiative (PMI), Bill & Melinda Gates Foundation (BMGF), World Health Organization, PSI, Ministry of Health (MoH)/ National Malaria Control Program (NMCP)-National & Sub-National levels, In-country Research Partners , Community Group Representatives, Civil Society Organizations (CSOs), Commodity Logistics Managers, Clinicians, Community Health Workers & Unitaid Staff.

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4 Findings

The evaluation results are summarized in Fig 1.0 below. Detailed findings thereafter have been structured by evaluation **Criteria** and *evaluation questions*.

Fig 1.0 DAC Assessment Overview

Criteria	Not achieved	Slightly achieved	Moderately achieved	Largely achieved	Fully achieved	Strength of Evidence	Feedback (gaps in achievement)
Relevance *(Did the intervention do the right things?)*						*Medium*	Intervention was relevant to beneficiary needs. There were however project design gaps including study design/measurement limitations, missed observations at baseline and limited adaptation of project ToC.
Coherence *(How well did the intervention fit with other interventions?)*						*Medium*	The project fit well within existing systems and as a result inherited weaknesses of these systems. The project was unable to effectively leverage other resources to address these gaps.
Effectiveness *(Did the intervention achieve its objectives?)*						*Strong*	The project effectively delivered RAS, but was unable to connect beneficiaries to the required continuum of care.
Efficiency *(How well were the resources used?)*						*Strong*	The project was cost and time efficient and implementation arrangements worked well, there were challenges with delineating accountability for the project from the larger iCCM programs in-country.
Impact *(Did the intervention show public health & economic benefits?)*						*Medium*	The original project study design was limited and could not accurately measure impact per select impact indicator-CFR. Also due to the inability to connect beneficiaries to the required continuum of care after RAS administration impact was low.
Sustainability *(Will the benefits last?)*						*Medium*	The project is poised to be sustainable with funding already secured for scale up in DRC and Uganda but not fully secured in Nigeria. In addition, in all countries, delivery mechanisms and scale up funding are however heavily donor dependent and may not be adequate for long-term sustenance.

Supporting documents for strength of evidence:
Medium – document review, and key informant interviews
Strong - document review, key informant interviews and secondary data analysis and/or site visits

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4.1 Relevance

R1. To what extent did the objectives and design of the projects respond to the needs of targeted beneficiaries? (vulnerable populations, children, community and civil society organizations, government/national health systems, scale-up partners)?

The design of the projects, their objectives and expected results were **very responsive** to the current needs of targeted beneficiary countries, non-project countries, other malaria endemic countries and other global stakeholders.

4.1.1 Severe Malaria, Persistently High Mortality Rates & High Burden Countries

Malaria has persistently been one of the leading causes of morbidity, mortality and lost economic productivity in the past decade in Sub-Saharan Africa[11]. Despite a myriad of efforts to increase progress towards universal coverage with malaria prevention and case management interventions and commodities, the disease still claims over 400,000 deaths annually, most of which are children under 5 (67%) and pregnant women and in areas where access to health facilities is challenging.[12] The three target beneficiary countries have a disproportionately higher burden of malaria cases and deaths. Introducing an effective pre-referral treatment for children less than 6 years of age that can be administered at community level can be game changing in tackling severe malaria as it has the potential to reduce mortality rates in communities with limited access to health facilities[13] and the intervention strategically fills a unique gap in countries' national malaria reduction plans. [14]

Caregiver and child, Kole District, Uganda

4.1.2 Limited WHO Operational Guidance

Though the WHO recommendation on RAS use has been in place for over a decade, it came with limited operational guidance, so there is a gap in understanding the operational feasibility of the intervention in real-life settings and within existing health systems structures. This project was designed to fill this gap**.** The project plan included operational research across these three highly endemic countries to test the hypothesis that it is feasible to achieve reductions in severe malaria case fatality rates by delivering RAS through established integrated community case management (iCCM) platforms, supported with a minimal set of interventions to fill country health systems' gaps.[11] This evidence will also be transferable to a variety of African settings and is intended to inform WHO's operational guidance.

> *"In real-life settings, little was known about how this should best be implemented, all the information about the efficacy of RAS is from only one RCT" Global respondent*

4.1.3 Pre-existing Country Interest

Prior to the project, 16 countries had already included the use of pre-referral rectal artesunate in their national guidelines even though there were misalignments with WHO guidelines.[23] Some of these countries were also already procuring non-quality assured RAS products. The political will and

[11] Gallup JL, Sachs JD. The Economic Burden of Malaria. In: Breman JG, Egan A, Keusch GT, editors. The Intolerable Burden of Malaria: A New Look at the Numbers: Supplement to Volume 64(1) of the American Journal of Tropical Medicine and Hygiene. Northbrook (IL): American Society of Tropical Medicine and Hygiene; 2001 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK2624/

[12] World malaria report 2020: 20 years of global progress and challenges. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO .

[13] WHO Guidelines for the Treatment Guidelines of Malaria. First Edition. 2006

[14] CARAMAL Project Plan

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ownership already existed, thus there was an inherent level of preparedness across these countries to introduce, implement and scale up the intervention.

R2. Have design and implementation approaches been appropriately adapted/course-corrected to respond to any changes in context? Did the implementation address the important gaps in the response provided? Are there any outstanding work within Unitaid's mandate that would require further attention? Are all elements of the program's theory of change(ToC) still valid, how has it been adapted/revised through the life of the project?

The CARAMAL project faced a number of challenges that tested its design and implementation approaches, a number of these were addressed with slight modifications to implementation approaches, but the program design and its accompanying theory of change was not revised. There are however some critical issues that remain unaddressed mostly because they are beyond the scope of the project. These challenges, adaptations made and outstanding gaps are described below:

"It was not a randomised control trial where you have a control arm and treatment arm. In this project, we had what we called the pre-RAS period and the post RAS period and with all the confounding factors, it was really complicated to tease out the effect of RAS."
Global respondent

4.1.4 Pre-Post Study Design

The pre-post study design of the CARAMAL project; with Pre-RAS and Post-RAS phases and no comparison groups in either phase, had its limitations. The pre-post study can show temporality, suggesting that the outcome (Case Fatality Rate) is impacted by the intervention, however, it has no control over other elements that are also changing at the same time as the intervention is implemented. Therefore, the changes in fatality during the study period cannot be fully attributed to the intervention.

4.1.5 Baseline Assessments Gap

The CARAMAL project was implemented in two phases; a baseline phase called the pre-RAS period and an implementation phase called the post-RAS phase. Prior and subsequent to each of these phases, critical data collection activities were conducted to understand gaps that informed implementation. This provided an opportunity for the project to be adapted and course-corrected especially in response to contextual changes. The baseline assessments revealed two key gaps that were deemed addressable within the scope of the CARAMAL project; one was a lack of training on severe malaria case management among referral facility health care workers and the other was limited/uncertain availability of injectable artesunate. The project successfully addressed these gaps during the design and finalization of its planned supportive interventions prior to its implementation phase.[15,16] The baseline assessment however did not identify any challenges with availability of the full oral course of Artemisinin-based Combination Therapies (ACTs) which eventually became a critical challenge to showcasing the effectiveness of the project. The project was unable to address this gap as procurement of ACTs were out of scope and coordination with other supply partners in-country, unfortunately, did not yield the expected results in terms of ACTs availability.

4.1.6 Minimum Low-cost Sustainable Interventions vs. Significant Health Systems Investments

There were two elements in the CARAMAL project's theory of change that were proven to be invalid and created gaps in the delivery of the program. These were: 1) The assumption that the project will be implemented in areas where iCCM platforms and referral systems would be generally well functioning and as such would only require minimal interventions to ensure that RAS can be responsibly introduced; and 2) That referral facilities would be stocked with other commodities required to manage severe malaria patients. Through the course of implementation, the project team realised how suboptimal the health systems in implementation areas were. The minimal supportive

[15] CARAMAL Annual Report 2017
[16] CARAMAL Annual Report 2018

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interventions were grossly inadequate to fill the gaps identified and the level of investment required was beyond the scope of the project. Efforts were made to fill these gaps through collaboration with health systems governance units and other implementation partners. These efforts are described in more detail under **4.3 Effectiveness**.

4.2 Coherence

C1. To what degree does the CARAMAL project fit with other interventions (e.g., iCCM, Integrated Management of Childhood Illness (IMCI), etc, within targeted countries, sectors or institutions?)

The CARAMAL project was designed to fit within the health system and leverage existing structures. The project was **integrated almost seamlessly,** from guidelines and training curricula to planning, personnel, service delivery and supply mechanisms. The Supply Side grant was also coherent as it fit very well and was complimentary in meeting the CARAMAL project's product prequalification, commodity registration and availability needs. The Supply Side grant created valuable and productive connections between the CARAMAL project, manufacturers and the WHO PQP.

4.2.1 Integration of RAS in iCCM: Guidelines & Service Delivery

The CARAMAL project's planning and implementation was done in collaboration with Ministries of Health (MoH) at both national and subnational levels. The primary point of integration for the RAS intervention was within the iCCM program. The RAS intervention cuts across both iCCM and Integrated Management of Childhood Illness (IMCI) programs, and even though both programs have RAS included in their manuals they only covered children under 5 years of age, so there is inherently a gap for children between age 5 and 6 years[17]. The CARAMAL project however only focused on children under 5 so this had no effect. Another gap with integration with the existing ICCM is that iCCM programs focus on equipping CHWs to provide quality care at the community level, not strengthening referral mechanisms or quality of care at referral facilities. The project therefore had to include supportive interventions to strengthen severe malaria case management at referral facilities in a bid to fully integrate the RAS intervention and its accompanying cascade of services[14].

4.2.2 Co-creating Trainings, MoH Facilitators & Supervisors

The coordination and partnership with MoH included the co-creation of the training curriculum and sub-national level training plans to ensure integration of the training within the countries' iCCM curriculum. MoH trainers also served as facilitators and subsequently supervision teams consisted of designated MoH supervisors in each implementation area.[11,15]

4.2.3 Leveraging Logistics Management Systems

Each of the CARAMAL project countries leveraged existing logistics management systems for RAS. In Adamawa State in Nigeria, there is one central medical store and three zonal stores for decentralized warehousing of medical commodities and supplies and RAS was managed through this system. The Uganda national medical store was also used to store and distribute RAS within existing storage and logistics management systems in place for iCCM commodities. In DRC, agreements with the Global Fund principal recipient Santé Rurale (SANRU) created a shared supply management system for malaria commodities.

4.2.4 Linking CARAMAL, Manufacturers and WHO

The Supply Side grant was also coherent and was designed to be so, by virtue of its supportive role. MMV also provided technical support to manufacturers, guiding them through the WHO PQP. It also created relationships between manufacturers and countries working closely with the CARAMAL teams to facilitate in-country registration of the new QA RAS products.

[17] Rectal Artesunate Landscaping Assessment Report

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C2. How well does the intervention align with priorities/needs identified by partners/the global disease response?

4.2.5 Global Disease Response Goals, Strategies & Focus Countries

> *"The aspect of improving access to care at the community and reducing mortality is completely aligned with how we support case management in-country" Global respondent*

The intervention aligns very well with the needs of partners and priorities of the global disease response; clearly aligning with the Sustainable Development Goals to end HIV, TB and Malaria, and the WHO's global technical strategy for malaria 2016-2030 to accelerate progress towards malaria elimination. The CARAMAL project is also working with three project countries that are designated as high burden and high impact with respect to the global disease response. This alignment highlights the value of this project to the disease response, especially with providing evidence on the operationalization of RAS in real life settings as well as additional perspectives on case management barriers and understanding how other supportive interventions can be better used to address those barriers.

4.2.6 Global Coordination & Information Sharing Across Country and Global Stakeholders

The projects also interacted with a large selection of global stakeholders through alignment meetings with the malaria team at PMI to understand country malaria operational plans; and meetings with Global Fund in-country teams to leverage synergies and support countries to plan for the next funding cycle (NFM3 2020 – 2022 Medicines for Malaria Venture (MMV) and the Clinton Health Access Initiative (CHAI) convened a Severe Malaria Global Stakeholder Meeting, under the auspices of the RBM Case Management Working Group and in collaboration with UNICEF, Swiss Tropical and Public Health Institute (Swiss TPH) and Médecins Sans Frontières (MSF). The meeting was hosted by the Nigerian Ministry of Health in Abuja, Nigeria and held on the 21st and 22nd of October, 2019.

This was the first meeting convened on severe malaria case management, building on stakeholder meetings focused on Injectable artesunate (Inj AS) and artesunate rectal capsules (ARC) in 2011 and 2016, respectively. The meeting assembled countries that have commenced the process of rolling out rectal artesunate within their systems of severe malaria care and was also aligned with the Roll Back Malaria (RBM) Case Management Working Group. This meeting helped bring countries on board as well as align the intervention with the priorities of key national level and global stakeholders.

4.2.7 Leveraging Other Donor Funded Partners & Projects in Project Countries

The alignment with other partner's work in CARAMAL project countries was especially prominent with Global Fund initiatives. For instance, the three health zones targeted in DRC are also beneficiaries of the Global Fund, as such the CARAMAL project, in collaboration with the Global Fund PR-SANRU, harmonized their supply chain to provide malaria commodities to these health zones.[18] The project also benefited from UNICEF's co-funding in each of the project countries; The European Union funding for iCCM activities, non-malaria iCCM commodities, and ACTs procurement, as well as Global Fund financed ACTs in Nigeria; and also the UK Foreign, Commonwealth & Development Office (FCDO) supported iCCM implementation, including the procurement of RDTs and ACTs in Uganda.[17]

C3. To what extent is the CARAMAL project adding value (and not duplicating efforts or establishing parallel systems)?

4.2.8 First Large-Scale Study, Seeking to Introduce RAS at Scale in Real-World Settings

[18] CARAMAL Semi-Annual Report 2018

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The CARAMAL project's unique value proposition is it's evidence creation with respect to the project's five core research questions which include understanding if the introduction of pre-referral QA significantly reduces suspected severe malaria case fatality rate under real-world operational circumstances in these three diverse settings; understanding what the minimum requirements are for a community case management system to ensure that is an effective part of the continuum of care from community to referral facility level; understanding if the introduction of RAS promotes the use of a monotherapy treatment against uncomplicated falciparum malaria and what interventions are necessary to avoid this inappropriate use; and lastly understanding the unintended consequences of scaled implementation such as adverse drug reactions, unforeseen costs and associated costs and cost-effectiveness of the intervention. For WHO, the wealth of learnings from the CARAMAL project will be key in the development of an operational field guide to support RAS implementation and continued refinement of severe malaria guidance.[19] [20]

"There are several interesting pieces that will come out of the CARAMAL study because it's a huge pilot across several countries and it's done with rigour, we'll be able to borrow a lot of learnings and try to use them to influence our work with other countries." Global respondent

4.3 Effectiveness

*E1. To what extent did the projects achieve their objectives and expected outcomes in **addressing targeted access barriers** within the specified timeframe and budget?*

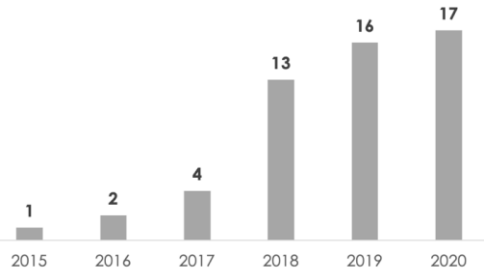
The projects increased access to QA RAS as part of strengthened severe malaria management systems by overcoming three major access barriers: Quality, Demand and Adoption, as well as Supply and Delivery. The sections below provide a detailed synopsis on how each of the access barriers were addressed.

4.3.1 Quality

E6. To what extent has the Supply Side grant contributed to increased availability of RAS that are commercially available for rapid introduction in LMICs? Have the products supported through the two projects been registered for commercial use in relevant project countries or are plans in place for their registration after project closure?
E7. How successful was the Supply Side grant in bringing quality-assured RAS for adoption in LMICs? To what extent has the Supply Side grant contributed to the evidence base facilitating regulatory approvals/market authorization? How has the Supply Side grant contributed to the approval (by WHO PQ or another appropriate regulatory authority)?

Having at least one QA RAS product registered in each of the project countries is a precondition to proceeding with generating evidence on the impact and responsible use of RAS. At the start of the projects there was no QA 100 mg RAS product, although two manufacturers, Cipla and Strides, had submitted dossiers to the WHO-PQP. Both manufacturers also submitted dossiers to the Global Fund Expert Review Panel (ERP) in Q1 2016, and ERP approval was granted to Cipla in December 2016 for a 12-month period.[33] The Supply Side grant worked closely with manufacturers to achieve quality assurance for their products through technical assistance that included risk mitigation, review of dossier submissions and supporting manufacturers to prepare for

Fig 2. Cumulative Number of Countries that have Registered RAS



[19] Community Access to Rectal Artesunate for Malaria (CARAMAL) Project Annual Meeting Report, October 26, 2020
[20] CARAMAL Annual Report 2019

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WHO PQ Good Manufacturing Practice (GMP) inspections. These efforts resulted in the 100mg RAS products from Cipla and Strides receiving World Health Organization (WHO) prequalification in February 2018 and June 2018, respectively. Registration of QA RAS in project countries was achieved through expert consultations, post submission follow-up and close monitoring of manufacturers to meet approval body requirements. The 100mg RAS products from Cipla and Strides secured regulatory approval in DRC in June 2017 and September 2017, respectively; in Nigeria in January 2019 and October 2019 respectively; and in Uganda both products received approval in November 2018. QA RAS has also been registered in several non-project countries, with the number of country registrations increasing from 4 at project inception to 17 countries at the time of this evaluation.

4.3.2 Demand and Adoption

E8. What progress did the CARAMAL project make in facilitating increased demand and uptake for scale-up of cost-effective RAS products within target countries and beyond? How effectively have implementers partnered with/engaged and supported communities and civil society organizations to increase demand, political support and financial commitments? How effective have the implementation generated demand and the ability to reach the priority target population.

4.3.2a Co-creation of BCC Interventions & Leveraging Existing Tools

Community engagement was critical to ensuring that RAS is accepted and adopted for use among patients and CHWs across all three project countries. The CARAMAL project worked closely with the Ministries of Health to design context-specific strategies with a goal to improve care-seeking behaviour among community members, promote the use of RAS among CHWs and encourage completion of treatment among caregivers. Activities focused on civil society engagement included the development of key messages and targeted community dissemination through heads of households, mothers, local associations, and religious networks; strategic placement of posters; and opportunistic use of local radio and community events[21]. As such, CSOs were engaged in the CARAMAL project to help achieve the necessary awareness creation, demand generation, and acceptance of RAS in the target communities. More specifically, CSOs contributed to the development and pre-testing of BCC materials to ensure they would be suitable for the local context and appropriate for the targeted communities. They were also involved in the mobilization of caregivers and key opinion leaders in the communities. CSO propagated positive messages about RAS, and thus increased acceptance and spurred demand for RAS across communities. The CARAMAL project adapted and operationalized the educational tool kit and BCC materials developed by MMV in project countries.[22]


CHW, Care Giver & Child Kenge District, DRC

4.3.2b Assessing and Course-correcting BCC Interventions

The CARAMAL project's baseline household surveys also informed BCC interventions; these assessed treatment-seeking patterns, caregivers' knowledge of and attitudes towards RAS, socioeconomic status and other community characteristics related to malaria. The project implemented these cross-sectional household surveys annually in study areas.[17] The assessments revealed that BCC interventions were not particularly effective in DRC; at improving awareness of RAS or demand for it. To address this, the project in partnership with the MoH conducted workshops that focused on

[21] Civil society Engagement Matrix, 2018
[22] MMV training materials available on SMO: https://www.severemalaria.org/toolkits-training/rectal-artesunate-tools-training

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revisiting and revising communication messages and approaches, including a reassessment of media and tools used for communication activities in close consultation with local stakeholders. The assessment concluded on the need to utilize additional platforms to promote the use of RAS including theatre, churches, and marketplaces; as well as the need to involve local authorities in decisions on how best to engage specific communities. Due to COVID-19 pandemic, some behaviour change communication (BCC) activities in DRC (e.g., community dialogues) were temporarily discontinued. In Uganda, BCC platforms were leveraged to communicate integrated messages on malaria and COVID-19.[23]

We have many success stories within the communities where we work. Community members nicknamed the pre referral RAS "Intervention Rapide" as their testimony to how effective RAS was….CHW

4.3.2c Overall Effectiveness of Demand Creation Interventions

In general, the cross-sectional household surveys showed a high acceptance of RAS in communities and among health workers across the three countries. However other indicators on the effectiveness of BCC interventions showed mixed results, for instance 83% of children (<5years) with suspected severe malaria received QA RAS administered by CHWs (90% in DRC, 82% in Uganda and 61% in Nigeria. However, only about half of these children go on to complete the referral, and subsequent post referral treatment with an oral course of ACTs dwindles to very low levels in Uganda and Nigeria. Referral completion and post-referral treatment rates were however higher in DRC at 61% and 71% respectively. These last two indicators were incredibly hard to shift considering the socio-economic conditions in project locations, and that the project did not provide any extensive support to facilitate transportation of patients or procure ACTs for patients. The projects engagement with national malaria control programs (NMCPs) in non-project countries Angola, Liberia, Madagascar, Sierra Leone and Benin, also resulted in increased demand for QA RAS beyond the 3 project countries.[17] The support provided to these countries and scale up results are discussed in more detail in sections **4.3.14**, **4.3.18** and **4.6.4** below.

"In both Angola, and Sierra Leone for example, historically, there has been some hesitancy on the behalf of the Ministry of Health to put RAS in the hands of community health workers for various reasons. The technical expertise through workshops, training and reports from CARAMAL countries now serve as advocacy tools." Global respondent

4.3.3 Supply and Delivery

E9. To what extent did the grant improve supply and delivery systems to ensure that products reach those in need in a reliable and timely way? To what extent did the two projects contribute to establishment (or integration) of functional and sustainable supply chain processes, including forecasting, planning, procurement, storage, and distribution? To what degree has the grant ensured that systems are put in place to mitigate diversion, wastages and other forms of losses due to supply and delivery inefficiencies?

4.3.3a QA RAS Commercially Available

Receiving WHO PQ status is a key milestone in commercializing a product, ensuring global availability as well as inclusion on the Global Fund procurement list.[24] The projects improved global supply of quality assured RAS and made them commercially available for in-market consumption. The three project countries received requested quantities of either suppliers' product to fulfil the CARAMAL project's requirements throughout the life of the project. From the CARAMAL project's inception till December 2020, 126,904 units of RAS were procured across the three project countries and 91,189 units distributed to CHWs and peripheral healthcare workers. Supervision efforts and enforcement of

[23] CARAMAL Semi-Annual Report 2020
[24] Supply Side Grant Plan

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the use of 100mg QA brands also helped flush out non-QA RAS from previous procurements within project countries.

4.3.3a Supply Security

The first supply challenge that the projects faced was supply security of quality assured products due to a halt in production of RAS by Cipla in 2018. The halt was due to adjustments in the manufacturing process at Cipla, which required WHO approval before further RAS production. This was however a challenge that was anticipated by MMV during the design of the Supply Side grant, thus the prequalification of two suppliers instead of one. The PQ concern was therefore easily resolved by placing all orders during this period with Strides. Strides also had some challenges including expiry of API, but were still able to deliver within timelines that didn't adversely impact project activities.[15] The COVID-19 pandemic also impacted manufacturers' production processes as they had not automated their production line for RAS at the time. They had to have fewer personnel on production lines to allow for adequate social distancing and this reduced their packaging speed and resulted in some late deliveries. Minimal levels of stockouts of RAS within the range of 1%-14%, were reported by CHWs and peripheral healthcare workers.[17] These were related primarily to in-country distribution challenges.[22] These reduced remarkably as the project gained momentum in all three countries.

4.3.3b Functional & Sustainable Supply Chain Processes

The CARAMAL project worked with the relevant government mechanisms to support forecasting, procurement, storage, distribution and stock monitoring of RAS.

- **Challenges:** One of the first challenges was quantifying a new product without any past consumption data, this resulted in inaccurate quantification which resulted in expiries as the project erred on the side of oversupply.[25,26] Optimizing the efficiency of distribution systems to ensure no stock-outs and delivery of commodities to those in need in a reliable and timely way was one of the most critical supply chain processes on this project. The project needed to distribute RAS to CHW in hard-to-reach areas, ensure RAS was kept below 30°C or exchange left over stock every 4-6-months due to the potential degradation of the product. In Uganda, extreme rainfall reduced accessibility to certain areas. In some project locations distribution to CHWs only took place quarterly during review meetings, in others, there was the expectation that CHWs would pick commodities from the health facilities; a number of CHWs were volunteers and unpaid staff and didn't have the resources to make this trip. The supply and delivery systems for RAS were already complex with accessing hard to reach CHWs, temperature requirements, exchange processes and extreme rainfall in some locations, however this was further complicated by the COVID-19 pandemic in 2020, with warehouses prioritizing COVID-19 supplies at the expense of RAS and other iCCM commodities; and typical avenues for distributing supplies interrupted. Pandemic restriction related challenges were however short-lived. The project experienced both over and understocking of RAS, but still kept stockouts below projected targets through the activities listed below:

> *"The distribution of medicines/RAS to community health workers is not necessarily very clear. The medicines don't get to them through a clear path, for instance, community health workers need to go find the medicines that they need at health facilities" Country level respondent*

[25] Community Access to Rectal Artesunate for Malaria (CARAMAL) Project Annual Meeting Report, October 26, 28-30 2020.
[26] Supportive Supervision Reports 2019

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- **Coordination:** The CARAMAL project worked closely with the designated country procurement and supply chain management (PSM) teams to ensure consistent supply by the integration of QA RAS into national drug supply systems including the existing iCCM supply systems for CHW and supply systems for peripheral health facilities. A small technical working group met regularly to complete the procurement, supply and distribution plans and present them to a larger group of stakeholders for review before being finalized and implemented.

- **Temperature/Exchange Requirements:** Initiatives taken to address RAS temperature requirements, in project locations where temperatures above 30°C are seen almost all year round and refrigeration facilities and electricity are very limited; Included storing the product in earthen pots buried underground which acts as a natural refrigerant, and leveraging supply chain processes for other commodities to increase the frequency of distribution of RAS. RAS was included in distribution of routine vaccines or added to other non-government/donor supported supply chains to fast-track distribution.

"We were guided by WHO to replace the RAS stock every four to six months in cases where the ambient temperatures would regularly exceed 30 degrees. The process was found to be very impractical, leading sometimes to health workers getting very small stocks." Country level respondent

- **Adapting to the Pandemic**: During the early months of the COVID-19 pandemic, supervisors were engaged to take commodities to the field during supervisory visits and review meetings were conducted in smaller clusters where feasible. By June 2020, the normal distribution processes through review meetings had resumed with COVID-19 prevention guidelines in place.

- **Additional Distribution Support:** In other cases, throughout the life of the project where distribution systems were deemed unable to reliably deliver medicines to CHWs and peripheral health facilities, the CARAMAL project did not try to remedy the national distribution system, but instead facilitated the distribution of MoH commodities (ACTs, Injectable Artesunate) alongside QA RAS to the implementation areas through alternative mechanisms. For instance in DRC, the project leveraged the Global Fund programme supply chain and in some cases the field team from the Kinshasa School of Public Health (KSPH) helped monitor and distribute RAS stock at community level during their field activities. In Uganda, the project leveraged the work of NGOs (Malaria Consortium and Regional Health Integration to Enhance Services (RHITES) Project) to support commodity redistribution. These parallel approaches are not sustainable but were necessary to maintain RAS stock levels.

- **Capacity Transition:** In its final year, the CARAMAL project observed ministry officials actively incorporating the learnings from CARAMAL, including those related to commodity availability. There has been an increase in stock monitoring frequency for case management commodities including RAS, across countries, with Uganda monitoring stock status on a weekly basis. The pipeline for RAS, injectable artesunate and other malaria commodities is now full, and forecasts are reviewed on a quarterly basis in Uganda. In Nigeria, the country has allocated additional funding for injectable artesunate procurement as part of its Global Fund request as well as Adamawa State level procurement plans through their Drug Revolving Fund (DRF). The DRF will require out of pocket costs so it isn't the optimal solution, but it will at least ensure availability of case management commodities which was a critical gap on this project. There have also been frequent reforecasts, qualifications alongside LMIS monitoring through LGA and state-level Logistics Management Coordination Unit (LMCUs) in Nigeria. In DRC, the Programme National de Lutte contre le Paludisme (PNLP) requested additional funding from Global Fund to place emergency orders to supplement planned order levels.

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4.3.3c Losses

The CARAMAL project's RAS forecasts relied upon multiple data sources, including incidence data from routine health information systems: specific data on the number of patients and types of illnesses seen by the existing iCCM programs, and published information on malaria cases and fatality rates. Accurately quantifying RAS needs was a challenge, as the number of severe febrile cases seen at peripheral facilities was unpredictable and data on true severe disease rates in the community were typically unavailable**.** As a result, there were cases of wastage experienced across project countries mostly due to overstocking. Once RAS was fully rolled out, the project addressed the overstocking issue through the use of a resupply tool that utilized consumption data, this helped health workers determine their actual need by monitoring consumption patterns and stock levels. This also helped minimize losses due to expiry of excess stock. The other reason for wastage was the stability profile of the product at high temperatures (>30°C); the projects in collaboration with the WHO PQP initiated an additional activity that retrieved RAS from community health workers and tested the stock in a medical laboratory in Switzerland. The projects assessed the level of degradation in order to determine if RAS could be kept for longer at these temperatures due to real world constraints and potentially eliminate the need for these routine exchanges. The results led the WHO-prequalification team to amend its guidance, now recommending that replacement is only indicated at 6 months.[27] [28]

E2. What were the main factors influencing the achievement or non-achievement of the intended outputs or overall outcomes?

There are several factors that have been influential in the achievement as well as non-achievement of project objectives. These factors are representative of the realities of introducing a new product like RAS into an existing community health system under real-world operational circumstances. This section describes the key factors.

Factors that positively influenced achieving the projects objectives

4.3.4 Targeted Supportive Interventions

The CARAMAL project leveraged existing systems and processes for training, supervision and service delivery. During its integration process, existing personnel, processes and resources were assessed and corresponding supportive interventions were implemented to fill the identified gaps per project scope. Some of these intervention areas include:


Healthcare Worker, Care Giver & Child Fufore LGA,

- **Community Health Worker & Referral Health Provider Capacity:** This was a supportive intervention area identified during baseline assessments. The assessments revealed that not all the facilities had staff with the capacity to manage a severely sick child. The use of existing government health workers at both community and referral level for service provision, training facilitation and supervision was critical to successfully integrating the intervention. However, the additional support provided to train and retrain CHWs and peripheral healthcare workers on pre-referral treatment of severe malaria and subsequently case management at referral facility was a critical success factor considering the significant skill gaps

[27]https://extranet.who.int/pqweb/sites/default/files/MA123part1v1_0.pdf
[28] ttps://extranet.who.int/pqweb/sites/default/files/MA124part1v2_0.pdf

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reported at baseline (In Nigeria 54% of facilities lacked any personnel that had been trained on severe malaria case management[29]; in Uganda only 23% of facilities had a medical doctor trained on severe malaria, and 59% of facilities had a nursing officer trained on severe malaria.[30] DRC was the only project location that had adequate numbers of qualified and recently trained health workers in severe malaria case management[31]).

- **Routine Health Information Systems:** The information systems at community level were also weak so it was impossible to capture every potential severe malaria case as originally intended. This also affected the ability to monitor the performance of CHWs. Working through in-country research partners; Kinshasa School of Public Health, Makerere University and Akena Associates, the CARAMAL project set up a parallel research data collection system which was very robust and covered data on patient treatment seeking, patient referral, health workers' skills, commodity availability and patient outcomes. However, such a parallel system is not expected to be replicable. The CARAMAL project planned to pare down the system based on experiences from the project to a set of parameters and modes of collection that are more feasibly implemented during scale-up. The project intends to provide guidance on this as part of its evidence for operationalizing RAS. There was however a noteworthy integration effort in Uganda, where the CARAMAL project engaged with the MoH, local cellular network providers, and local regulatory bodies to be able to tap into the existing mTrac electronic system for reporting key health indicators by SMS. The mTrac system was extended to allow CHWs to report individual cases of severe febrile illness as well as aggregate weekly case counts.[17]

- **Injectable Artesunate Availability:** The baseline health facility assessments also identified limited/uncertain availability of injectable artesunate across all project countries as earlier mentioned. The CARAMAL project included this commodity in its procurement plan as a critical supportive intervention, and as a result over 80% of children who completed referral received injectable artesunate across all project countries.

4.3.5 Authorising CHWs to Administer RAS

This has been a longstanding view amongst health care professionals and it was also observed within the project. There was some hesitancy among senior health officials to allow CHWs implement RAS, citing that community health workers do not have the capacity to diagnose severe malaria, as well as fears of misdiagnoses due to limited access to RDTs. These concerns were well addressed through the CARAMAL project's capacity building efforts as described above in **4.3.4.**

4.3.6 Stakeholder Collaboration & Evidence Dissemination

The strong collaboration between the CARAMAL project consortium, the Supply Side grant and other partners in project countries at country and global levels was an important success factor. Sharing best practises through the Severe Malaria Observatory website, meetings and workshops improved coordination, visibility and immediate opportunities to begin to add value to non-project countries and other global programs.

[29] CARAMAL: Rapid assessment of referral health facilities in Adamawa State, Nigeria 2018
[30] CARAMAL: Rapid assessment of referral health facilities in Uganda 2018
[31] Rapport de la mission conjointe effectuéedans les Zones de Santé de Kenge, Kingandu et Ipamu 2018

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Factors that negatively affected the delivery of the projects' objectives

4.3.7 Integration Challenges

Leveraging existing systems and processes for training, supervision and service delivery was both an advantage and disadvantage. The intervention was well integrated within the MoH structures in the three countries, but also inherited the existing weaknesses of these systems ranging from inadequately trained health workers to weak supply chain processes and sub-optimal referral systems.

"RAS is not a magic bullet; it is a small part of a larger cascade of services to manage severe malaria" Country level respondent

- **Referral Systems:** The project identified the need to work across both iCCM structures and referral health facilities since iCCM programs primarily focus at community level, not on strengthening referral mechanisms or the quality of care at referral health facilities. In response to this, the project ensured that supportive interventions included severe malaria case management strengthening at referral facilities by leveraging relationships with hospital management authorities or hospitals directly. The challenges with sub-optimal referral systems was addressed through the introduction of bi-directional referral slips and expanding emergency transport systems to include children under 5 (Nigeria only) and utilizing motorcycles (DRC only), however a significant portion of referrals remained uncompleted or unreported. Gaps in referral systems were largely not addressed by the project as significant investments in this area were beyond the project's scope, but also because a major factor at play here were socio-economic characteristics of beneficiary communities.

- **Logistics Management Systems:** The project experienced both understocking and overstocking of RAS, as well as stock outs of other essential commodities for malaria treatment. At the beginning of the project, there was low utilization of RAS by the CHWs, therefore some eligible children did not receive RAS. This is mostly due to complexities with rolling out a commodity that is required by a very specific subset of the community (children under five with severe malaria) but had to be distributed across a vast number of health workers within struggling ICCM systems, with its temperature regulation requirements and 4-6 month exchange process. Challenges with the supply chain have been discussed extensively in **4.3.3b** above.

- **Donor Supported Structures:** The project also found that even though the goal of integrating with iCCM was to leverage government systems within countries towards eventual countrywide scale up and sustainability of the intervention through government resources, the reality was that many elements of the iCCM programs in countries were donor supported. As a result, integration and collaboration efforts of the project went beyond working with the government structures and stakeholders to leveraging and lobbying other partners and donor systems and structures to fill health systems gaps. This will ensure short term sustenance of project efforts, but in the long term, financial resources will need to be identified to enable expansion and sustainability.[14]

"The first fragility was building on an ICCM platform that was financed by other donors. It started to be a house of cards that was trying not to topple over on itself". Global respondent

4.3.8 Minimal Supportive Interventions

The CARAMAL project is not a health systems strengthening project, so it only planned to provide low touch support referred to as "minimum low-cost sustainable interventions" in the project plan. These supportive interventions were evidence-based and determined based on baseline health systems assessments and household surveys completed in the first year of the project (The Pre-RAS Phase). The baseline assessment however didn't identify some of the critical health systems gaps, neither did

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it provide adequate validation for selected sites (sites were defined in the project plan as relatively well functioning), as a result the final set of supportive interventions were inadequate to address the gaps and therefore limited the effectiveness of the intervention. In addition, the magnitude of supportive interventions that could potentially fill some of these gaps such as community referral systems were resource intensive, most likely unsustainable and would be beyond the defined scope of the project. There was however lower hanging fruit that could have been addressed such as availability of ACTs.

"It wasn't supposed to be a health system strengthening project, we were to introduce the project with a few tweaks to the system here and there. We now know that minimal tweaks are not going to get the job done"
Country level respondent

4.3.9 The "Right"Care Seeking Behaviour

Moving the needle on care seeking behaviour has always been challenging and often requires longer time frames for new interventions. Behaviour change was even more difficult to tackle on this project. These communities have lived with malaria for so long and didn't see it as dangerous, so providing a pre-referral treatment that had instant results somewhat reinforced the poor care seeking behaviour. When a caregiver decided to seek care from the CHW and received RAS, it was more likely that the caregiver would not complete referral for the child resulting in monotherapy and incomplete treatment.[32] Also caregivers who felt the case of their child was serious, often bypassed the community health worker heading straight to the referral hospital or other private sector providers (which is actually good care seeking behaviour if they were able to access the facility in time). The project assessed its BCC interventions through annual surveys and made course corrections as earlier described in **4.3.2b**

4.3.10 Monotherapy

Due to inadequacies in the health system, resulting in incomplete referrals, The CARAMAL project contributed to artemisinin monotherapy and also uncovered existing artemisinin monotherapy in the health systems in these countries. The evidence generated by the project clearly shows availability of injectable artesunate which increased during project implementation, with over 80% of children admitted at referral health facilities receiving this as per WHO treatment guidelines. This is one point at which monotherapy occurred, as many of these children do not go on to receive the full course of ACTs afterwards.[28] The other point where monotherapy occurred is at the community level with children receiving RAS not completing referrals and being less likely to continue the follow-on care as compared to those who didn't receive RAS. A few sub-national level respondents reinforced this evidence with a referral facility health worker expressing relief at the reduced workload due to treatment provided by CHWs in the community and CHWs being excited that they can now treat patients in the community with seemingly little concern about supporting clients to complete referrals. This was more prominent in Uganda and Nigeria. In DRC, CHWs described how happy they were with the quick response after RAS administration, severe malaria signs improved significantly in a short timeframe and caregivers and communities were so satisfied they nicknamed RAS *"Intervention Rapide"*, a term used to designate special police units called upon to respond to distress calls from victims of crime. CHWs in DRC also described difficulties getting parents/caregivers to complete referrals and how they used parents of past patients who completed treatment as role models for others in their communities to emphasize the need to complete treatment through sharing their experiences. These were referred to as *"Parents Modeles"* (exemplary parents).

4.3.11 Ambitious Implementation Timelines

The CARAMAL project design per the project plan was very robust, and thought through all the key areas of implementation; addressing both demand and supply side needs and foreseeing potential risks that could impact success. A most impressive element of the project plan was the level of detail put into integration efforts, anticipated supportive interventions as well as transition and

[32] CARAMAL Annual Report 2020

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sustainability planning. The project also identified an appropriate set of results and performance indicators. The downside however was the very ambitious project timeline. It is not uncommon for projects to have a goal to reduce mortality, especially for interventions that are proven to directly reduce mortality like RAS. The challenge with the CARAMAL project was the expectation that this could be achieved in just under two years. The project was planned to be a three-year project, but its first year was a baseline year and therefore implementation of RAS did not start till year 2 during which there was a somewhat gradual rollout (as expected) in the first 6 months before all CHWs had adequate quantities of RAS and most eligible children began receiving it. So, the project essentially had the intervention fully implemented for about 18 months. This short implementation timeframe coupled with the enormous health systems deficits almost made it sure that the impact of RAS in terms of mortality reduction would not materialize. A longer time frame may have increased the chances that certain critical implementation challenges would have been smoothed out and become relatively well-functioning. Putting in place referral systems through procurements of vehicles and motorcycle ambulances would have been extremely resource intensive to introduce and manage. It is also well beyond the project's scope to improve the economic circumstances of beneficiaries which is a major barrier to completing referral. However, ensuring the consistent availability of ACTs for children who complete referral could have made a substantial difference. This was a lower hanging fruit that could have been achieved with time. The links between these unresolved health systems gaps and the project results are discussed in more detail in **4.4.2.**

4.3.12 Contextual Challenges- COVID-19, Ebola, Elections & Unpredictable Weather

There were a number of contextual challenges experienced during the life of the projects, these ranged from the COVID-19 pandemic to an Ebola outbreak in DRC, elections in Nigeria and DRC, and weather changes (extreme rainfall in Uganda) in the implementation phase. The **Ebola outbreak** in DRC caused significant disruption to the health system in the country due to a shift in health care resources towards addressing the emergency, however, project implementation areas were not directly affected, so the impact was manageable. **Protracted election processes** in DRC and Nigeria caused political instability, this however only affected some community engagement activities that were delayed so as not to be mistaken for political rallies.[33] A **warehouse attack** in Nigeria resulted in the loss of RAS products. There was also massive **flooding** in Nigeria which increased **displaced populations** and very high levels of **rainfall** in Uganda, factors that contributed to increasing malaria cases. **COVID-19** restrictions presented challenges for RAS distribution especially with respect to deliveries to CHWs, as routine processes for resupply were interrupted in all project countries. The project enabled redistribution between facilities when stocks from central warehouses had not arrived. The project also identified alternative mechanisms for resupply of CHW in all 3 countries, such as engaging supervisors to take commodities to the field during supervisory visits and conducting review meetings in smaller clusters. The engagement with non-project countries' NMCPs in Angola, Liberia, Madagascar, and Sierra Leone was also disrupted due to COVID-19, the project however utilized virtual engagements subsequently.

E3. How was the implementation approach effective in promoting global policy adoption and country adoption both in project and non-project countries?

4.3.13 Ongoing Evidence Dissemination

As earlier described, the projects regular engagement with WHO, ongoing dissemination of preliminary findings, sharing experiences, insights and best practices with national and global audiences will be a very important factor in informing global policy adoption.[17] There is already a positive trend with more and more countries adopting RAS and donors already committed to procure RAS. A critical result here however would be the finalization and release of the WHO field

[33] CARAMAL Semi-Annual Report 2019

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implementation guide that the project was designed to inform. Study results were however still being analysed at the time of this evaluation.

4.3.14 Continuous Country Engagements

Country level policy and guideline changes have been an ongoing activity from the early days of the project. The CARAMAL project supported the update of national strategic plans to include RAS and associated interventions in all three project countries. The strategic plans for DRC and Uganda have been approved, the plan for Nigeria has been finalized since September 2020 but still awaiting approval. Both projects also engaged directly with NMCPs in Angola, Liberia, Madagascar, and Sierra Leone and Benin to strengthen severe malaria case management through review of country severe malaria plans, training materials, as well as virtual workshops[17]. These country engagements also involved collaboration with the President's Malaria Initiative (PMI) and other implementing partners in these countries. Through December 2020, the project has facilitated the revision of 5 national guidelines of non- project countries (Ghana, Rwanda, Sierra Leone, Tanzania, Zanzibar) to align with WHO guidance, thus resulting in 18 countries with WHO aligned guidelines. The project is already seeing government's buy-in across these countries through guideline and policy changes. The constant engagement between government, CARAMAL implementers, other donors and other stakeholders through the life of the project was the critical factor for success in this area. The process towards country level and global policy adoption is well underway, with further analysis to finalize the critical body of evidence from the CARMAL project still ongoing.

> *" It is like the train on the rail, we know pretty much where it's going to go, and there is no doubt that it's going to have a significant impact in the very near future." Global respondent*

E4. How effective was the implementation in driving and catalysing the global market and supply in terms of volume and prices?

4.3.15 The Price of RAS

At inception, the CARAMAL project implementers expected that QA RAS would be at a slightly higher price than the non-prequalified products, however the price of the product is still below $1. The Supply Side project worked strategically with manufacturers early on to provide technical support and had a very strong influence in the price setting of RAS. Utilizing MMV's deep insights into the malaria market and evidence-based costing, the Supply Side project guided manufacturers on target prices whilst keeping RAS affordable. The CARAMAL team also indicated that the volumes procured through this pilot were insufficient to reduce the price over the course of the project. Even though the current price is already quite low and price is not necessarily a barrier for RAS, the project expects that prices will reduce once sufficient volumes are achieved through scale-up after this project is completed[34].

4.3.16 Profitability of RAS

Manufacturers acknowledge the low price of RAS and its comparatively small procurement volume. Despite this, they seem motivated to support this work as part of their corporate social responsibility and contribution to the malaria response. They alluded to making very little profit and making significant investments to automate the production systems for this commodity which resulted in much lower return on investment as compared to other malaria commodities. It will be important to implement additional measures to incentivize and sustain suppliers.

4.3.17 Leveraging other Donor Funding for Scale-Up

The introduction of RAS as a pre-referral intervention in project countries is generating evidence on rational use, acceptability, safety and affordability of the intervention and this evidence is already informing scale-up in project countries as well as stimulating other non-project countries to plan

[34] RAS_ProjectPlan_Amendment1

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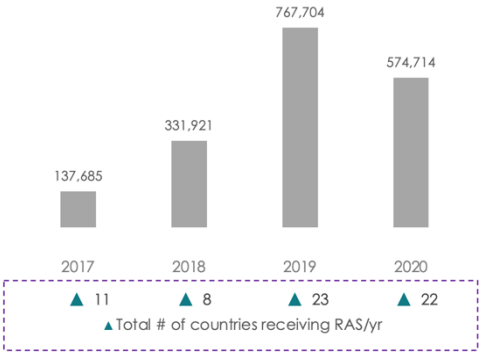
appropriate introduction and scale up of QA RAS. Beyond domestic sources, the core sources of RAS procurement are PMI and the Global Fund and each of these funders have seen increases in the number of countries showing interest in and procuring RAS. These funders require alignment of national guidelines with WHO and of course procurement of a quality assured product as prerequisites for funding. Although the CARAMAL and Supply Side projects are not the only factor responsible for the increase in RAS procurements, it is very clear that both projects contributed significantly to this, through making QA RAS available through the two prequalified manufacturers; working with countries to update their guidelines to include RAS in alignment with WHO guidelines, and engaging country Ministries of Health towards the incorporation of RAS in their proposals to these other donors.

4.3.18 Increasing Procurement of QA RAS

The commodity only became available in 2018 and has seen more and more countries procuring the quality assured 100-milligram formulation beyond the three project countries. In 2020, 22 countries procured this commodity based on supplier annual sales reports to WHO. Over 700,000 and 500,000 (packs of 2 caps) were procured by 23 and 22 countries in 2019 and 2020 respectively, compared to just over 100,000 procured by 11 countries in 2017.

"There is a substantial increase in the procurement and availability of RAS" Global respondent

Fig 3. Quantities of QA RAS Supplied by Manufacturers Annually



4.3.19 Defining RAS at Scale

Successful scale up of a product like RAS, is not just about the disease burden and the availability of the commodity, since it simply won't make a substantial difference without the required cascade of services. The key limitations to getting RAS to scale include the available community health workforce in countries; the complexity of the supply chain processes especially the 4-6month exchanges in settings with temperatures higher than 30°C; prioritization of CHWs in favour of higher-level referral facilities by caregivers in areas with limited access to health facilities; and the availability of systems to deliver post referral care. *When 80% of CHWs consistently have an adequate and viable supply of RAS to serve children who are greater than 6hrs away from any health facility, and at least 80% of eligible children are administered RAS, and 80% of these complete referral and receive post-referral care, then we can say RAS has gone to scale. This definition is based on the CARAMAL project targets and learnings.* The availability and delivery of RAS alone is simply not enough.

4.4 Impact

Im1. To what extent has the CARAMAL project generated, or is expected to generate Public health and economic impact at the national and global level. To what extent has the CARAMAL project promoted equity. What additional benefits has the health system experienced due to the introduction of the project? What unintended effects have been experienced as a result of the project to either beneficiaries or the health system?

Public Health & Economic Impact

4.4.1 Direct Impact

The intervention's impact could not be accurately measured in terms of Case Fatality Ratio (CFR) calculations based on its original pre-post design as this was limited by a myriad of contextual challenges in the post-RAS implementation phase. The project intended to roll out the RAS

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intervention and determine what implementation would look like in real life settings with a goal to reduce deaths among children with suspected severe malaria that are seen at the community level in implementation areas. The CFR for children enrolled by community-based providers (CHWs and peripheral health facility staff) across the three countries was 2% in the Pre-RAS phase and 4% in the Post-RAS phase. This ratio did not take into account confounding factors such as seasonality, case severity and completing post-referral treatment (including COVID19-restrictions impact on care seeking behaviour) all of which have been established to be associated with mortality. This comparison was also based on the limited pre-post design as earlier described. These will however be addressed in the final study report to be released by the project in mid 2021. In addition to the seeming increase in CFR, the project also experienced an increase in Malaria prevalence in all three countries during the post-RAS phase. The CFR increase in DRC was not as pronounced as in the other two countries. The increases in mortality were also not statistically significant, so the RAS intervention cannot be said to increase mortality.

4.4.2 Understanding the Increase in CFR

It is however important to understand the seeming increase in CFR seen on this project due to its goal to serve as an important body of evidence for RAS implementation and scale up in real-life settings. A critical finding in all 3 countries was that mortality increased in both community enrolments as well as patients directly attending referral facilities, this points to the potential effect of contextual factors. Other data also showed limitations to the effectiveness of the intervention in real life settings that could also explain the high fatality rates observed. A review of data on care at referral health facilities in Nigeria and Uganda where the increase in CFR was more dramatic, found that only a minority of children were administered ACTs at the facility after receiving parenteral treatment with artesunate. Furthermore, Uganda's day-28 follow up tests showed many healthy (60%) and sick (80%) children testing positive for malaria. In Nigeria, 94% of children followed up on day-28 were reported as healthy, 58% of these had a positive RDT and 100% of those reported sick had a positive RDT result.[17] [35] The increase in malaria prevalence, poor referral and treatment completion rates as well as the day-28 follow up results provide a relatively straightforward explanation for the mortality rates seen on the project. As said earlier the increase in mortality is unrelated to RAS, but these additional evidence indicate major gaps in the severe malaria case management continuum. RAS is efficacious, but when integrated in sub-optimal health systems its contribution is limited.

"The referral system was one of the hardest nuts to crack". Global respondent

"We knew that children are unable to complete the referrals because they live too far from the facility or don't have money to get transport to the facility. " Country level respondent

4.4.3 Potential Indirect Impact

The potential impact of the projects was however estimated through modelling by the evaluation team. The evaluator's modelled estimates show that the projects could contribute to 47,152 [0 – 68,381] lives saved and 2.7m [0 – 4.0m] DALYs averted from 2020-2026 across Africa. The projects will confer an incremental cost of US$57m [49m, 63m] to the health system, with an average cost of US$34 [32,37] per child receiving RAS. The public health impact of RAS, however, will result in positive productivity gains/net savings and a very high ROI. The impact value ranges indicate the possibility of not achieving impact, with the zero value and the negative net cost representing scenarios where follow up services post-RAS implementation are not available, resulting in increased costs to the health system without any commensurate public health benefit.

[35] CARAMAL Executive Summary Presentation to Unitaid November 2020

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4.4.4 Equity

The CARAMAL project targeted children less than 5 years of age who are seeking treatment for suspected severe malaria at the community level and cannot reach a facility in less than six hours[36]. Many of these children with severe malaria and their caregivers 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 their inability to promptly seek care, leading to delays in receiving a full and effective course of treatment, increasing the risk of mortality[19]. The three focus LMICs are also highly endemic and accounted for 39% of malaria related deaths in 2019. These countries also have significant health systems gaps.

"RAS as a recommendation from WHO is specifically for people who do not have access to quality health facilities. That is the point of this product, is to keep your child alive long enough that you can get to this very remote facility. In that sense, I think equity was at the core of the project " County level respondent

4.4.5 Strategic Benefits and Positive Externalities

The CARAMAL project set out to roll out the RAS intervention, however it uncovered significant health systems gaps and their impact on severely ill children, increasing knowledge on why there has been a stagnation in malaria mortality and providing evidence on the care seeking pathway for severely ill children. As discussed throughout the report there were substantial gaps in referral services for children with severe malaria who received RAS. In DRC the health authorities did make significant efforts to improve referral systems as evidenced by project results; they collaborated with community structures to engage commercial motorbikes operators at a shared cost to the health system and to the communities. The motorbike operators were contacted as needed by CHWs to provide transport to the referral facility. This resulted in improvements in completing severe malaria referrals as well as referrals to other services.

"CARAMAL can now provide a good, rational narrative, and an explanation of why we are stagnating in terms of malaria mortality and morbidity. That's really a huge positive externality from this project. The CARAMAL project has brought countries to a stage where, they are much better informed than they were 3 years ago." Global respondent

In addition, the project also developed a complementary CARAMAL artemisinin resistance marker monitoring protocol, based on discussions previously held with WHO. Its purpose was to measure the prevalence of molecular markers of artemisinin resistance in *Plasmodium falciparum* before and after the introduction of RAS and tentatively assess whether the introduction of RAS is associated with an increase in the selection of strains carrying resistance markers.[14] An unexpected finding of this study was the identification of parasites with resistance markers in the project areas, particularly in Uganda. It was clear from the data that this resistance could not have been a result of the RAS implementation simply because of the short implementation period. This was really an important finding, indicating artemisinin resistance, potentially through the use of injectable artesunate and the non-completion of therapeutic courses of ACTs and/or purchase and use from the unregulated sector which includes poor-quality and counterfeit ACTs.

4.5 Efficiency

Ef1. How timely, cost-efficient and cost-effective was implementation including allocative efficiency and technical efficiency?

[36] RAS_ProjectPlan_Amendment1

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4.5.1 Time-efficiency

The CARAMAL project experienced delays in signing the contract and receiving funds from Unitaid, this resulted in delays in project start up. Subsequently the project received bi-annual disbursements which included a four-month buffer as is Unitaid's standard practice ensuring that implementation was well covered within disbursement periods. The initial delay at start up resulted in tight timelines between funds disbursement, ethical approval and field activities kick off. There was little room for unanticipated delays in the process of obtaining ethical approval or in the implementation of field activities. This resulted in certain activities being implemented concurrently instead of sequentially, an example was the rollout of the Patient Surveillance System while field testing of tools was still in progress,[20] this did create some inefficiencies but had little to no effect on the program.

The catalytic design of the project also meant that the project was expected to leverage existing systems, which is excellent for fostering ownership and sustainability. It however introduced some inefficiencies with respect to implementation timelines. In cases where multiple activities are funded by other donors, the project had to wait for these pieces to align, for example incorporating RAS trainings into iCCM trainings supported by another donor meant that the RAS training would not start until the other donor's preparatory processes for the iCCM training were completed. These delays were however infrequent.

4.5.2 Cost-effectiveness

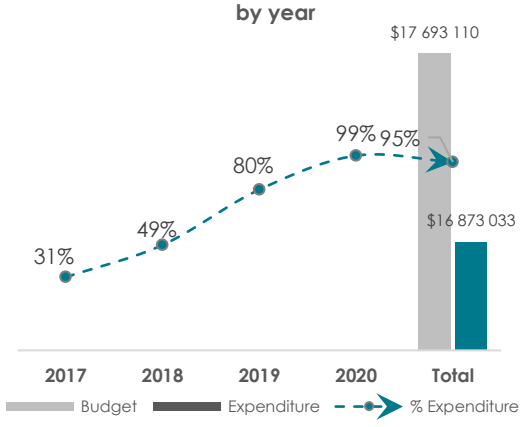
The project is currently conducting a costing exercise to estimate the average real-world costs of RAS introduction. These estimates will include provider-level implementation and health system strengthening costs, household and out-of-pocket costs, and societal costs. The implementation cost by country exercises will be refined to identify the estimated split between RAS-related and other health system strengthening costs. The intention of the costing exercise is to guide resource allocation and identify economic barriers to treatment access.[21] The results of the costing study were not available at the time of this evaluation, but are expected to be released by the project by mid 2021. Pre-referral artesunate treatment is however already proven to be a cost-effective, life-saving intervention, which can substantially improve the management of severe childhood malaria in rural African settings in which programmes for community health workers are in place[37].

Ef2. What factors have been considered to ensure that value for money has been achieved from an efficiency standpoint? Comparing immediate deliverables against the expenditure.

4.5.3 Cost-efficiency

The CARAMAL project's absorptive capacity increased annually from a 31% burn rate in 2017 to 99% in 2020. The lower budget consumption in its first year was due to protracted ethics review processes and late receipt of its first-year funding, however the project increased its budget consumption annually, in tandem with the scale up of project activities and was proactive in adjusting and realigning budgets each year. The project subsequently received approval to utilize the savings generated through the project life to cover a six-month

Fig 4: Expenditure as % of annual budget, by year



[37] Yeşim Tozan, Eili Y Klein, Sarah Darley, Rajashree Panicker, Ramanan Laxminarayan, Joel G Breman, Prereferral rectal artesunate for treatment of severe childhood malaria: a cost-effectiveness analysis, The Lancet,Volume 376, Issue 9756, 2010

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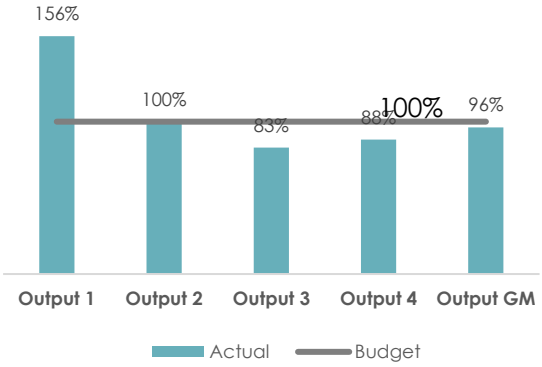
extension period from November 2020 to April 2021. A review of expenditure by output as at December 2020 showed underspend across all outputs except output 1 that was overspent by 56%, due to under budgeting RAS procurements in Nigeria, and the mistaken omission of RAS from the 2019 budget for DRC. The overspend on Output 1 was compensated for by underspends across the other outputs. The CARAMAL project however, completely delivered all of its planned activities across all outputs on schedule.

Fig 5: Expenditure as % of total budget, by output



The factors the project considered to achieve value for money started from the design of the project streamlining the consortium and working in 3 countries where implementers had established in-country presence; Integrating the intervention within existing health systems structures, and leveraging other partners and donor funded activities in project locations. These have been discussed extensively throughout this report already.

Ef3. Was the funding allocation/split to cover commodities/supplies versus other costs efficient to achieve project objectives? What best practices, if any, could be learned for similar grants in the future?

4.5.4 Optimal Funding Split

The funding split across outputs was optimal and was sufficient to complete activities per the program design. RAS is a comparatively cheap product, costing less than $1, so there was really no issue with the sufficiency of the commodity allocation. Implementers were satisfied with the budget allocations and the flexibility of Unitaid to move items across budget lines where necessary.

An increase in the budget for supportive interventions under Output 2 to include additional activities especially the procurement of ACTs was likely to have enabled the project to show the effect RAS can have on reducing mortality among severely ill children despite the other contextual challenges faced.

Ef4. How well did the grant implementers collaborate with national authorities in project planning, implementation and assessment to promote integration into existing health systems?

4.5.5 Co-working with Government Authorities

The project team has made a concerted effort to ensure that national and sub-national level authorities within the project countries are supportive and actively engaged throughout the life of the project, as this is critical to a successful transition and subsequent nationwide scale up of RAS. At inception, the project was introduced to national and subnational government stakeholders in each of the three countries, which helped gain their buy-in and facilitated smooth implementation. In each country, the project also supported the creation and convening of RAS advisory committees that provided strategic guidance and support for implementation throughout the duration of the project. The project participated in relevant TWGs and related meetings in each country and held project led dissemination meetings that shared preliminary findings. Lastly there were also global meetings at project start up in June 2017 and subsequently in October 2019 in partnership with MMVs Supply Side grant; these created opportunities to foster

"it goes back to how supervision was done, how distribution was done…. none of those pieces were standalone parallel structures that were implemented because of RAS. The intent of the project was to have it integrated into how the Ministry of Health was already operating its iCCM structure……So in that sense, the vision was for an extremely efficient project. " Global respondent

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cross-country collaborations and facilitate future coordination within and across project and non-project countries.

Ef5. To what extent was the implementation arrangement (including consortium structure) optimally designed to ensure efficient delivery of the project objectives

4.5.6 The Consortium Arrangements Worked

The consortium arrangements worked quite well. Each consortium partner played their respective role and there was strong collaboration and transparency. CHAI's leadership role was well executed ensuring effective communication and collaboration across members to achieve project results. It was also critical for interaction with stakeholders in non-project countries that already had a relationship with CHAI. CHAI also had a lot of past experience implementing pilot/demonstration projects that are scaled and sustained via the project's catalytic effect which was very critical for this project. All members applauded the excellent efforts of Swiss TPH to deliver on their assigned scope as they had little to leverage on and were building a robust research data collection system in very remote contexts. The ability to leverage close relationships with government structures, thereby enabling a somewhat seamless integration of the intervention into government systems was the biggest strength that UNICEF contributed. The implementation arrangements with respect to integrating the project and working through government structures had its disadvantages, these have already been discussed in **4.3.7**. In addition it became challenging when attempting to delineate accountability for this pilot from the larger iCCM program.

4.5.7 Coordination, Communication & Management

The project had a robust plan with respect to key operational practices to achieve effective partnership, these included: regular communication to discuss implementation issues and upcoming activities and events; joint programmatic meetings with all project staff to ensure alignment; and clear assignment of accountability for specific grant deliverables. These practices were integrated into the planning of the RAS Project and the structuring of the consortium roles and responsibilities.[11] The project initiated coordination activities through its project kick-off meeting June 2017 attended by all consortium members and supportive implementers. The meeting served as an avenue to introduce project members from each organization and country, clarify objectives, roles and responsibilities as well as set up mechanisms for project coordination, communication and management.[14] Subsequently, the consortium continued to engage frequently through the life of the project, ensuring communication and feedback loops were always closed and connecting with staff on the Supply Side grant and enabler grants as needed.

"Communication has been effective among partners as well as feedback to donors, manufacturers, and everybody else. For instance, when there were issues with stock outs, COVID-19 pandemic, we ensured that everyone was kept abreast by leading weekly and biweekly calls with all consortium partners and key global players such as WHO, PMI global Fund, MSF."
Global respondent

4.5.8 Supportive Projects

The CARAMAL consortium was very well complemented by the WHO and MMV, who performed supportive activities through the "WHO Enabler Agreement" and the "MMV Supply Side Grant''. These two projects interacted with CARAMAL on a routine basis, leveraging each other's strengths and networks, thereby resulting in a very productive working relationship and the delivery of shared outputs. The complementarity of MMV on the Supply Side grant was optimal, utilizing their relationships with manufacturers and their experience with the WHO prequalification process to achieve output 3 of the Supply Side grant and output 1 of the CARAMAL project. MMV also provided support for development of BCC/IEC materials that were adapted by the CARAMAL project, as well as

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the collaboration in non-project countries to influence guideline changes, register and introduce RAS. The project has also worked hand in hand with WHO to understand expectations and provide inputs into the field implementation guidance. The in-country research partners, University of Kinshasa in DRC, Akena Associates in Nigeria and Makerere University in Uganda also played a very critical role with their teams on the ground navigating really hard to reach project locations to collect study data.

4.6 Sustainability

S1. How has the CARAMAL project contributed to an enabling global environment for scale-up, including generating evidence, normative guidance, product supply capacity, tools to support country adaptation and uptake and advocacy, and stronger partnerships among global actors?

4.6.1 The Donor Landscaping & Scale-Up Plan

The project set up a Donor Landscaping Steering Committee in order to advise, critique, validate and provide data and information related to RAS that will create greater knowledge around the historical and future trends of RAS orders, procurement and uptake.[20] The project also coordinated its routine communication with major donors and buyers of QA RAS on the needs of project countries for this life-saving treatment. In partnership with the Supply Side grant, it also collected, analysed and provided data and information on RAS global market dynamics, suppliers, prices, customers and production and procurement perspectives to inform its scale up plan.

4.6.2 Ongoing Engagement with WHO & Global Stakeholders

The project's regular and continued engagement with WHO and global audiences to disseminate preliminary findings and share lessons learnt from its unique evidence collection is definitely its most significant contribution to creating an enabling environment. See more details in **4.3.5,** and **4.3.19**.

S2. To what extent has the CARAMAL project helped established country readiness for scale-up, including securing ongoing political and financial commitments by national governments and other partners, supportive policies and enhanced health system capacity for delivery, and partnering with communities and civil society to mobilize ongoing community demand and engagement?
S3. To what extent have core elements of the intervention been transitioned to ensure that the benefits of the intervention will continue beyond the life of the investment?

4.6.3 Country Readiness for Transition & Scale- Up in Project Countries

The severe malaria case management approaches (including RAS) were prioritized in all three national strategic plans (NSPs). The NSPs for DRC and Uganda have been approved, with the Nigeria NSP on track for approval in March 2021. The project also worked to update a number of national documents including the national treatment guidelines in all three countries, the essential medicines list in all three countries, national quantification plans in all three countries, national iCCM training materials in Uganda and DRC in line with global guidance. [17] [16]

The project has also worked with Ministries of Health towards the inclusion of RAS in relevant funding streams as well as within domestic budgets. All three countries included RAS and the required supportive interventions into requests to donors such as PMI and GFATM. For PMI this was the malaria operation plan in Q3 2019 and for Global Fund, concept notes were submitted in Q1 2020. In GFATM concept notes, Uganda requested two years of RAS supply for 61 priority districts, Nigeria advocated for scale up across 12 states, and DRC requested a three-year extension supported by a quantification to address previous supply shortages. The GFATM request from Nigeria was however not approved. Countries have also continued advocating to include RAS in other funding pots for example the World Bank Malaria grant for Nigeria. National level coordination groups such as the Malaria technical working groups, case management sub-committees and iCCM task forces in countries are now ardent

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advocates for RAS expansion and RAS is also being integrated into operational plans at subnational level. [20,21] Further strengthening of other malaria case management commodities, most notably injectable Artesunate and ACTs, will be required going forward to maximize the impact of RAS implementation. Improvement of existing M&E systems, which were previously flagged as a source of challenges, would allow for the impact of RAS to be reported.

To ensure smooth transition of the RAS project, the project conducted monthly TWG meetings with the NMCP, WHO, and other key stakeholders in-country to foster ownership of the project investments and ensure continued buy-in. The project also involved both national and subnational MoH staff in key project activities, including planning for project activities, conducting training and routine supervision.

4.6.4 Scale Up in Non-Project Countries

TThe project leveraged CHAI's relationship with project country governments to work closely with their MOHs to ensure all aspects of national scale-up plans are as appropriately planned as possible and that the MOHs are supported in this process. In 2019, the project engaged directly with the national malaria control programs (NMCPs) in Angola, Liberia, Madagascar, and Sierra Leone on strengthening severe malaria case management. In 2020, CHAI hoped to build on these engagements and expand support to additional countries, but these efforts were largely halted due to COVID-19. CHAI held preliminary discussions with the Benin NMCP and the President's Malaria Initiative (PMI) in Q1 2020 to understand their severe malaria plans, which include a large-scale rollout of RAS through CHWs. CHAI was able to provide some remote support to non-project countries during the reporting period (e.g., reviewing training materials for Sierra Leone) and is exploring opportunities to expand this type of support in the coming months, including a virtual workshop for Angola and potentially Liberia. The project is also working with MMV to explore alternative options for the second Global Stakeholders Meeting. Through December 2020, 18 country guidelines for RAS were aligned with global guidance.

4.7 Learning

L1. What have been the lessons learned and how have they been incorporated in the lifetime of the grants or across other interventions? Have lessons learnt been widely disseminated by grantees and Unitaid?

4.7.1 Multi-stakeholder BCC Efforts

The BCC interventions on this project were a critical component of implementation because the intervention cuts across a spectrum of stakeholders, at household, community, CHW/peripheral health facility, referral health facility and MoH levels. Ministry of Health officials and referral health facility specialists needed to buy-in to the idea that CHWs could administer RAS; CHWs had to adhere to guidelines and only administer RAS to eligible children; Caregivers and their communities needed to accept this rectal capsule- based intervention; Caregivers needed to immediately seek care for their sick child from CHWs instead of going directly to the higher level facility where travel times were protracted; and Caregivers needed to complete referral for their children and ensure they completed treatment even if symptoms were alleviated after RAS use. Behaviour change interventions must cut across policy makers, health workers and the community for RAS rollout to be successful.

4.7.2 Systems Rollout vs Product Rollout

A major lesson from this project is that a product rollout approach does not work for a product like RAS. The effectiveness of the RAS intervention requires a cascade of activities before and after the administration of the rectal capsule without which the intervention may be rendered ineffective. These include CHWs having viable RAS in stock; CHWs accurately diagnosing severe malaria; availability of referral mechanisms to ensure the child reaches the referral facility after the

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administration of RAS; ability of the referral health worker to manage severe malaria in children; and availability of Injectable Artesunate and ACT at the referral facility. The project identified this cascade early and attempted to resolve challenges at each step in the cascade. A number of these were moderately addressed, however availability and access to ACTs as well as completing referrals remained an outstanding issue.[28] These requisite health services must work in tandem with the behaviour change expectations earlier discussed. The graphic below shows the series of activities.

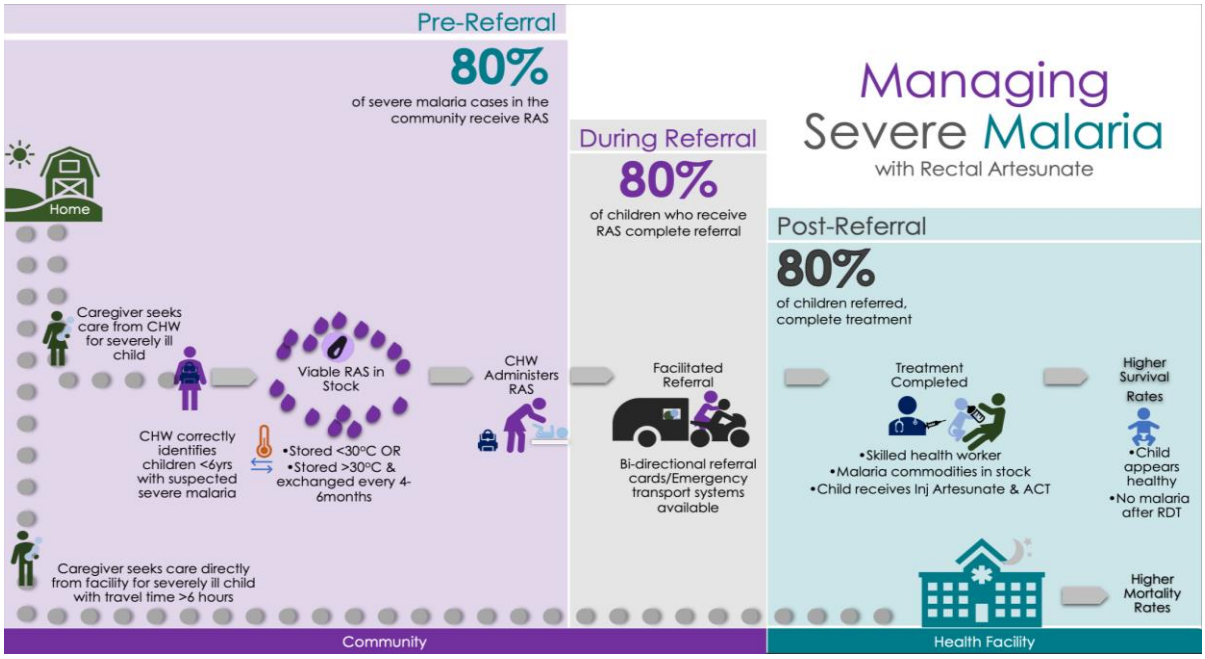

Figure 6: The CARAMAL Beneficiary Journey & Project Goals

4.7.3 RAS & Other Case Management Commodities

Solid progress was made against all three market access barriers with respect to RAS, however it seemed insufficient because other critical commodities such as RDTs, Injectable Artesunate and ACTs, must all be available for the program to be effective. Even with the lower level of referrals, the availability of ACTs at the health facilities would have made a huge difference. On reviewing data from the three countries, DRC was the only country where fatality (unrelated to RAS) did not increase dramatically, and even though it had a poor referral completion rate (57%), the ACTs completion was higher than the other two countries at 61%, underscoring the importance of a course of ACTs after RAS administration.

4.7.4 Temperature Regulation Innovations vs 4–6-month Swaps

Storage conditions at peripheral facilities must be monitored and innovative community temperature regulation practices like burying underground should be deployed to ensure storage of RAS products under manufacturer specified conditions and prevent product deterioration. The RAS heat stability study led to more relaxed guidance from WHO-PQ, recommending replacement of stock at 6 months in areas where the ambient temperature usually exceeds 30°C.

4.7.5 Opportunistic Evidence Dissemination

Communicating RAS project experiences, findings, and lessons learned via reports, manuscripts, donor fora, and conferences during project implementation, ensured that other countries with RAS in their guidelines were informed on best practices for use and implementation, and that malaria partners could advocate for the rational use of RAS on a global level. Communication of key lessons learned

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and best practices to key stakeholders at the national and district levels took place on a continuous basis via workshops of the national and district level RAS Project Advisory Groups (RAS PAG).

> ***"Health systems are never improved in a vacuum, they are improved off the back of needed interventions",*** *there is already political will in countries for RAS scale up, scaling up will increase focus on strengthening iCCM as well as community linkages and referral systems and these improvements will inadvertently increase the effectiveness of RAS in these real-life settings." Country level respondent*

4.7.6 The RAS Interventions as an Advocacy Tool

The project provided a better understanding of the implementation context of RAS in real-life settings and its integration requirements (improved referral systems, availability of other case management commodities, skilled workforce). These learnings alongside its life saving characteristics and potential impact on mortality can serve as a convincing argument for advocacy to governments towards improving health systems. RAS can potentially drive the change we want to see in these health systems.

4.7.7 Large Private Sector Role

One of the most important missed opportunities of this project was the exclusion of the private sector. In both Nigeria and Uganda, a large part of the population utilizes private sector providers, so understanding the role of the private sector in severe malaria management and care seeking behaviour is critical. The private sector must be engaged in rolling out RAS in these countries, for the intervention to go to scale.

4.7.8 Dissemination Platforms

The projects are already disseminating findings through a number of avenues and plans to continue disseminating findings after its close out.

a) **Project Documentation (Reports & Conference Abstracts):** Project experiences and evidence have been shared through 11 scientific/technical documents including the RAS landscaping report (2018), 7 baseline reports (2019), ASTMH presentation (2019), ECTMIH presentation (2019) and very importantly the CARAMAL scientific report completed as pre-read for WHO technical consultation (2021). The project plans for publications in scientific journals to commence in 2021. The Supply Side grant also evaluated the role that visible carefully targeted and delivered Information Education Communication (IEC) for community, caregivers and community health workers, may have in a real-life context. The findings from this study are also expected to help improve CHW diagnosis, treatment and referral of danger signs and in turn enhance prompt compliance with referral instructions by caregivers.[37] The ongoing RAS heat stability study will also inform future guidance on how to transport and store RAS to ensure it remains stable; this will also be disseminated in 2021.

b) Dissemination Events & Platforms: Project experiences and evidence have also been shared through:

- High-level Meetings and Seminars: These include the Multilateral Initiative on Malaria (MIM) conference 2018, Annual Meeting of the American Society of Tropical Medicine & Health (ASTMH) 2018, 2019 & 2020, three baseline review meetings in 2019, iCCM subgroup meeting in 2019, the European Congress on Tropical Medicine and International Health (ECTMIH) 2019 conference, Global Stakeholders Meeting 2019 and three midline dissemination meetings in 2020.
- RAS Project Advisory Groups: Communication of key lessons learned and best practices to key stakeholders at the national and district levels during the project life took place bi-annually through national and district level RAS Project Advisory Groups (RAS PAG).
- The Severe Malaria Observatory: The Supply Side grant launched the *Severe Malaria Observatory* in Q2 2017 in order to bring together materials from multiple resources as a repository of information related to severe malaria. The site aims to deepen global awareness and knowledge

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of severe malaria, provide severe malaria training materials and toolkits, and highlight ongoing activities. The observatory includes information on RAS and will provide a mechanism for sharing evidence and lessons learned through the CARAMAL project.

4.8 Risk Mitigation

L2. How effectively have strategic, implementation and sustainability/scalability risks been identified and managed over the course of implementation?

The project did a thorough risk assessment at design stages in order to identify an almost exhaustive list of implementation and scalability risks. The evaluation however will only discuss risks that the project experienced.

4.8.1 Strategic Risks

- The project had anticipated that severe disease rates and/or treatment seeking for severe disease at the community could be substantially lower than expected, and this had the potential to prevent significant evidence from being generated. The project addressed this by increasing the study sample size.

4.8.2 Implementation Risks

- **Service provision related risks** such as lack of robust referral systems in implementation areas leading to patients not completing their course of treatment and limiting the impact of QA RAS introduction; Low quality of care for severe malaria at referral facilities due to a lack of necessary commodities or a lack of capacity of healthcare workers; Interruptions to core funding for the iCCM programs in implementation areas; and COVID-19 delays and disruptions to service provision, refresher trainings and supervision activities. These risks were not fully addressed during the implementation period as most of these were out of the scope of the project except capacity building for health workers. These risks have a huge impact on the scalability of RAS intervention as seen by the reduced effectiveness of the intervention discussed earlier[38].
- **Commodity introduction risks** such as late country level regulatory agencies approval for the two prequalified RAS products. This can compromise the ability of project countries to receive timely deliveries. The CARAMAL project ensured regular follow up with the in-country agencies and the Supply Side project maintained regular communication with Cipla and Strides so that any potential concerns were flagged and addressed early. Also, RAS orders were placed with sufficient lead time such that deliveries can be made without impacting project timelines.
- **Commodity availability risks** included the challenging process for restocking of CHWs with RAS which was further complicated by the COVID-19 pandemic. The typical avenues for distributing new supplies were interrupted resulting in stock outs at the community level. The project identified alternative mechanisms for resupply, such as engaging supervisors to take commodities to the field during supervisory visits and conducting review meetings in smaller clusters.

4.8.3 Sustainability/Scalability Risks

- Substantial supportive interventions are required to ensure that QA RAS is appropriately used, and the lack of these additional interventions did inhibit the effectiveness of the intervention;
- Enabling conditions could not be met during the project life as they were out of scope, and will require significant effort for them to be met in continuation and scale-up. e.g. non-functioning referral systems and unavailability of commodities;

[38] CARAMAL project risk register

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- Use of QA RAS at the community level did not lead to the emergence and spread of artemisinin resistance, but study data revealed pre-existing artemisinin resistance most likely due to almost years consumption of ACTs in large quantities, sometimes of poor quality or counterfeit, and not complete adherence to 3-day course of ACTs. A smaller issue is might be associated with the lack of ACT treatment follow-up after injectable artesunate as project data shows high levels of injectable artesunate use without the subsequent completion of ACT. Contribution of RAS is deemed minimal given the very low quantities involved.

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5.Conclusions

The main conclusions of the evaluation are as follows:

The design of the projects, their objectives and expected results were very responsive to the current needs of targeted beneficiary countries, non-project countries, other malaria endemic countries and other global stakeholders. The persistently high burden and mortality rates in project countries, the availability of an effective pre-referral treatment that can be administered to children under 5 at community level, the gap in having a WHO operational guideline and pre-existing country interest are all factors that affirm the **relevance** of the projects. The CARAMAL project faced a number of challenges that tested its design and implementation approaches, a number of these were largely addressed with slight modifications to implementation approaches but the program design and its accompanying theory of change was not adapted, as a result some critical issues remain unaddressed and were for the most part beyond the scope of the project; these were the limited availability of ACT for treatment of children after referral to higher level facilities as well as the absence of supportive referral mechanisms /transportation systems or schemes.

The CARAMAL project was inherently **coherent**. It was designed to fit within the health system and leverage existing structures. The project was integrated almost seamlessly from guidelines and training curricula to planning, personnel and service delivery and supply mechanisms. The intervention also aligned very well with the needs of partners and priorities of the global disease response including the Sustainable Development Goals to end HIV, TB and Malaria, and the WHO global technical strategy 2016-2030 to accelerate progress towards malaria elimination. Furthermore it not only leveraged health systems, it also leveraged other donor funded partners and their projects. The Supply Side grant was also coherent as it fit very well with the CARAMAL project's commodity prequalification, registration and availability needs; it also created valuable and productive connections between the CARAMAL project, manufacturers and the WHO PQP.

The CARAMAL project was **moderately effective** with solid performance across most of its results areas.

- **Output 1 (Quality Assured RAS available in malaria endemic areas)** of CARAMAL project was implemented in tandem **with Output 3 (Improved global supply of quality assured RAS for management of severe malaria) of the Supply Side grant**. These outputs were completed successfully, with RAS products of the two selected manufacturers pre-qualified and approved for introduction in all project countries.
- **Output 2 (Rectal artesunate introduced as pre-referral treatment into strengthened severe malaria management systems in implementation areas)** was partly achieved, as the project successfully procured and distributed RAS to all target CHWs and health facilities, trained and retrained the target numbers of health workers and increased acceptability RAS in project communities, however critical health systems gaps impeded the consistent availability of RAS and other commodities as well as the ability of children who received RAS to be full treated.
- **Output 3 (Evidence generated and shared on effects and rational use of RAS)** was also completed successfully with evidence generated through multiple reports, conference presentations and abstracts and disseminated across multiple in-country and global platforms throughout the life of the project.
- **Output 4 (Transition to evidence-based and step-wise scale-up of RAS in target countries)** was also successfully completed through the inclusion of RAS in key strategic documents as well as in the Global Fund concept notes of all three countries. Through December 2020, 5 additional non-project countries updated their national policies on RAS to align with WHO guidance.

In relation to progress made toward **overcoming market access barriers,** we note the following:

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- **Quality:** The Supply Side grant introduced the first quality assured 100mg RAS products though WHO prequalification globally, available through two manufacturers. In-country supervision efforts were instrumental in flushing out non-QA RAS from previous procurements. MMV also worked closely with funders to ensure any country requests for non-WHO prequalified RAS strengths (50 and 200mg) products were replaced with 100mg RAS QA product.
- **Demand & Adoption:** The CARAMAL project facilitated increased demand and scale up efforts through co-creation of BCC Interventions with in-country stakeholders; leveraging existing IEC tools by MMV; assessing the effectiveness and adapting BCC interventions as necessary. These efforts however only achieved acceptance of the product, but did not really move the needle on care seeking behaviour. The CARAMAL project also increased adoption among non-project countries. The projects were very effective in positioning themselves to catalyse the global market, by working strategically with manufacturers to influence RAS price setting and leveraging other donor funds for scale up. There has been an increase in RAS procurements in project and non-project countries with 19 countries in sub-Saharan Africa and 3 others in Europe (distribution hubs) procuring this commodity in 2020 as compared to a baseline of only 8 in 2018. This could not have been achieved without the presence of these Quality Assured products
- **Supply & Delivery:** The Supply Side grant increased availability of RAS that are commercially available for rapid introduction in LMICs. Optimizing the efficiency of distribution systems to ensure no stock-outs and delivery of commodities to those in need in a reliable and timely way was one of the most critical supply chain process on this project. The project experienced stock outs ranging from 1%-14%, well below the projected target of 20%. The project ensured consistent supply by the integration of QA RAS into national drug supply systems including the existing iCCM supply systems and provided additional support to address supply chain gaps.

Overall, solid progress has been made against all three market access barriers with respect to RAS.

Through the successful completion of the projects' outputs and solid progress in overcoming the critical access barriers, the projects increased access to QA RAS as part of the severe malaria management systems. The main factors that influenced the effectiveness of the project were excellent stakeholder relationships at country and global level with multiple cross-learning platforms; integrating the program in existing systems thereby increasing ownership of RAS; and extensive capacity building efforts included in its supportive interventions.

The **impact** of the RAS intervention could not be measured in terms of CFR comparisons based on its original pre-post design as this was limited by a myriad of contextual challenges that made the project implementation phase very different from its baseline. The main drawbacks were the inadequate referral mechanisms and suboptimal supply chains and these were out of the CARAMAL project's implementation scope to address, but substantially limited the effectiveness of the intervention especially with respect to reducing CFR, as many children did not complete treatment at a health facility after receiving RAS. The CARAMAL project also had a very ambitious project timeline of reducing mortality in about 18 months of implementation.

The evaluator's modelled estimates show that the projects could contribute to 47,152 [0 – 68,381] lives saved and 2.7m [0 – 4.0m] DALYs averted from 2020-2026 across Africa. The projects will confer an incremental cost of US$57m [49m, 63m] to the health system, with an average cost of US$34 [32,37] per child receiving RAS. The public health impact of RAS, however, will result in positive productivity gains/net savings, with a very high Return on Investment (ROI). The impact value ranges indicate the possibility of not achieving impact with the zero value and the negative net cost representing scenarios where follow up services post-RAS implementation are not available resulting in increased costs to the health system without any commensurate public health benefit. Beyond the

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potential number of lives saved, the projects' beneficiaries were primarily vulnerable populations, including children under 5 who are the most susceptible to malaria, communities in high malaria endemic areas with limited access to health care, and governments of Low- and Middle-Income Countries (LMICs) with significant health systems gaps; depicting its heavy focus on equity and serving underserved populations.

In terms of **efficiency,** the CARAMAL project increased its budget consumption annually, in tandem with the scale up of project activities and was proactive in adjusting and realigning budgets each year. The funding split across outputs was optimal and was sufficient to complete activities per the program design. The factors utilized to achieve value for money included integrating the intervention within existing health systems structures, and leveraging other partners and donor funded activities in project locations. The project team has made a concerted effort to ensure that national and sub-national level authorities within the project countries are supportive and actively engaged throughout the life of the project. The consortium arrangements also worked quite well, with strong collaboration and transparency.

Lastly, the project is poised to be **sustainable**, with a very robust sustainability plan developed from its inception; a donor landscaping steering committee to create greater knowledge around the historical and future trends of RAS orders, procurement and uptake; regular and continued engagement with in-country TWGs, WHO and global audiences to disseminate preliminary findings and share lessons learnt; and technical support to project and non-project countries for strategic plan and guideline revisions, inclusion of RAS into essential medicines lists and iCCM structures as well as into requests to other donors such as PMI and GFATM. Funding is already secured for scale up in DRC and Uganda but not fully secured in Nigeria. The immediate commitments for RAS procurements in these countries are heavily donor dependent and will definitely ensure short term sustenance, but in the long term, financial resources will need to be identified to enable further expansion and sustainability. Achieving the full potential of the RAS intervention goes beyond securing funding for ongoing procurement, there must be commensurate support for addressing the health systems strengthening constraints earlier described.

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6.Recommendations

This section presents recommendations for different stakeholder categories based on lessons learnt under the projects.

6.1 National Malaria Control Programs /Ministries of Health

6.1.1 The RAS intervention needs to be viewed as a critical element of a larger package, so countries should **implement a systems rollout approach**. Countries should:

- Incorporate supportive interventions to enhance the delivery of Malaria case management (including RAS) in **national guidelines and strategic plans**. These should include considerable level of support for referral, the need for adequate stocks of RDTs, Injectable Artesunate and ACTs - especially these two latter commodities at the referral health facilities. - and a communication strategy specifically aimed at reducing the risk of monotherapy be it inj AS or RAS.
- Ensure RAS **baseline needs assessments** cover existing policies and guidelines, operational requirements (CHWs availability, referral obstacles, HCW training needs, supply chain gaps for RAS and related commodities, communication messaging), stakeholder engagements as well as considerations for funding and sustainability.
- Implement **supportive interventions that address the most critical gap** (CHWs availability, overcoming referral obstacles, ongoing HCW training needs[39], supply chain gaps for RAS and related commodities, communication messaging on monotherapy risks) in the severe malaria intervention cascade specific to each country to ensure that RAS is properly introduced in a continuum. While it is impracticable to expect a large-scale health systems strengthening intervention to rollout RAS – maximizing the full potential of the intervention will require consideration of certain elements in the continuum of care for severe malaria as being a pre-requisite to ensuring optimal community uptake, use and reductions in malaria mortality.
- **Plan jointly for availability of other case management commodities** (RDTs, Injectable Artesunate and ACTs) **at all levels of the health system**, with programmes closely monitoring the supply chains and stock levels of this set of commodities, not just RAS as this is critical to the effectiveness of RAS and preventing monotherapy.
- Develop PSM guidelines for RAS: This should include **clear processes for forecasting, distribution to CHWs, commodity exchange as well as the identification of temperature regulation options** (even the most rudimentary) as these are an important alternative to the somewhat complex commodity exchange systems required for this product, in areas where the ambient temperature usually exceeds 30°C.
- Set up **quality assurance systems** to ensure ongoing monitoring of artesunate monotherapy and resistance. Countries must also monitor the availability of poor quality and counterfeit ACTs and remove these products; and ensure that ACTs are responsibly used for the treatment of uncomplicated malaria including full adherence to the 3-day treatment to reduce the risk of resistance development.
- Develop a robust **communication strategy** specifically focused on addressing the risk of monotherapy with BCC interventions at patient and provider level.
- RAS rollout plans should **identify and prioritize sites in-country, where enabling conditions for RAS exist or could be rapidly bolstered** - including improving functionality of the health system - for the initial rollout phases. This will increase effectiveness, maximize learning and facilitate sustainability.

[39] https://www.severemalaria.org/toolkits-training/rectal-artesunate-tools-training

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- **Advocate for, and mobilize resources to support systems strengthening** (such as innovations to optimize referral systems, improve quality of community health data, BCC interventions at patient and provider level, as well as subsidized/free post-referral treatment in locations where RAS introduction is planned).
- Establish/leverage national **frameworks for private sector engagement** to integrate the RAS intervention as part of a robust severe malaria management plan, in countries where a significant portion of the population seek care from private sector providers. This will create opportunities for the private sector to be part of the planning and implementation of the RAS intervention.
- **Document lessons learnt and best practices** for program improvement and to inform further scale up. The project revealed the susceptibility of the intervention to a number of contextual challenges, so ongoing learning will be important for country implementers.

6.2 CARAMAL Project & Supply Side Grant Implementers

6.2.1 The unique value addition of this project is the robust body of evidence it provides towards real life implementation of RAS and a broader understanding of care seeking behaviour among severe malaria cases from the community level through to tertiary care. To ensure **comprehensive dissemination of final results**, implementers should:

- Leverage existing stakeholder forums and platforms for countries and other stakeholders to further engage with final project results even after project closeout is critical – particularly emphasising the need for supportive health systems with scale-up partners.
- Leverage the MMV hosted Severe Malaria Observatory (severemalaria.org) to disseminate detailed results
- Develop a quality assurance process for ongoing dissemination after project closeout.

6.3 Donors & Policy Makers

6.3.1 Future projects should include **RAS as a component of case management programs** as opposed to implementing a standalone intervention focused on RAS.

6.3.2 **Limit the number of pre-qualified manufacturers,** as the current procurement volumes are still quite small and may never increase to the level of other malaria commodities due to its specific target population (children under 6 with suspected severe malaria) and service providers (CHWs). Manufacturers also invest more resources in producing RAS than other malaria medicines, so any further reduction in the volumes of orders they receive due to splits across multiple manufacturers will make the venture unsustainable.

6.3.3 The upcoming **WHO field implementation guide should include guidance on** addressing the low referral completion and follow up treatment rates as well as the high monotherapy risk observed in the CARAMAL project. This may include specifications on how CHWs are networked with referral facilities, guidance on key messaging to address the RAS monotherapy risk and possible necessary adaptation to the iCCM guidelines as well as severe malaria case management guidelines and concomitant trainings.

6.4 Unitaid

In designing similar projects:

6.4.1 **Ascertain the validity of project design assumptions** during project baseline assessments, especially critical foundational implementation elements and impact measures. In this case the availability of relatively well functioning iCCM, referral systems and ACT availability.

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6.4.2 **Consider phased integration efforts** with a longer timeframe to address the most critical health systems obstacles or **implement in a formalized partnership with an existing health systems strengthening** project. In the current context of LMICs, health systems are still heavily donor reliant and sustainability right now looks more like an alliance with other donor funded programs than complete integration into national systems.

6.4.3 **Scope innovative opportunities that will enable referral pathways in LMICs with a robust sustainability plan,** especially for countries that experience significant access barriers. These can range from supporting community-managed emergency transport systems/schemes (ETS) for critically ill children, to subsidized treatment costs at health facilities.

6.4.4 **Consider evaluating different packages of supportive interventions / HSS conditions** that can inform country programs (e.g NMCPs) on how to implement RAS (or similar interventions) as part of a broader system, associated costs and impact of different packages. The evaluation design may comprise different study arms/groups that comprise the focal intervention (for example RAS in iCCM) with one or more supportive HSS interventions (for example HCW Training, BCC, ETS + Commodity Supply).

7. Risks, Limitations & Mitigation

7.1 COVID-19 Prevention Considerations

This evaluation was conducted during the COVID-19 pandemic and as a result contingency and safety measures were put in place. The safety of participants and interviewers throughout the data collection phase was assured by limiting the numbers of in-person engagements to the barest minimum, utilizing more virtual interviews/group discussions with key informants. Where necessary and absolutely unavoidable, one on one in-person interviews were conducted adhering to the Ministry of Health COVID-19 prevention guidelines in each country; using face masks, sanitizing hands, tools and surfaces and practicing social distancing.

7.2 Insecurity in DRC and Nigeria

The challenges with insecurity in DRC and Nigeria were identified early on with a plan to utilize virtual data collection methods. During data collection the evaluation the team monitored the security situation in these areas very carefully, relying on available security advisory. Site level visits were conducted in both of these countries with no incidents reported.

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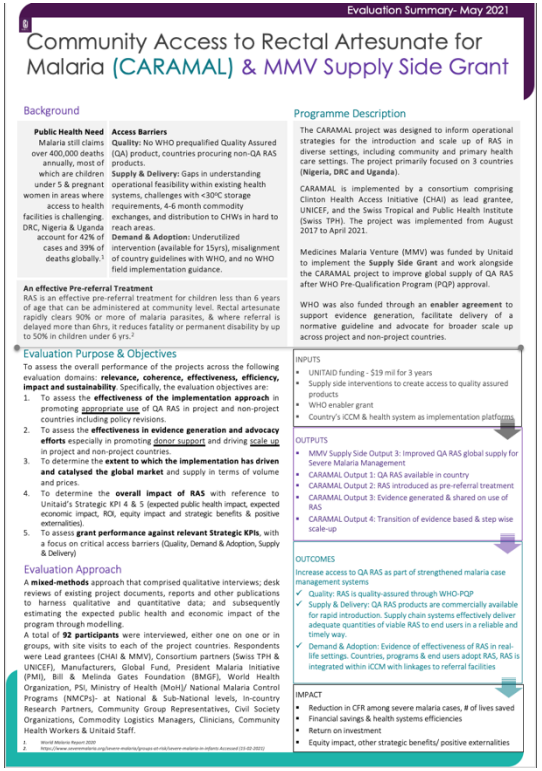
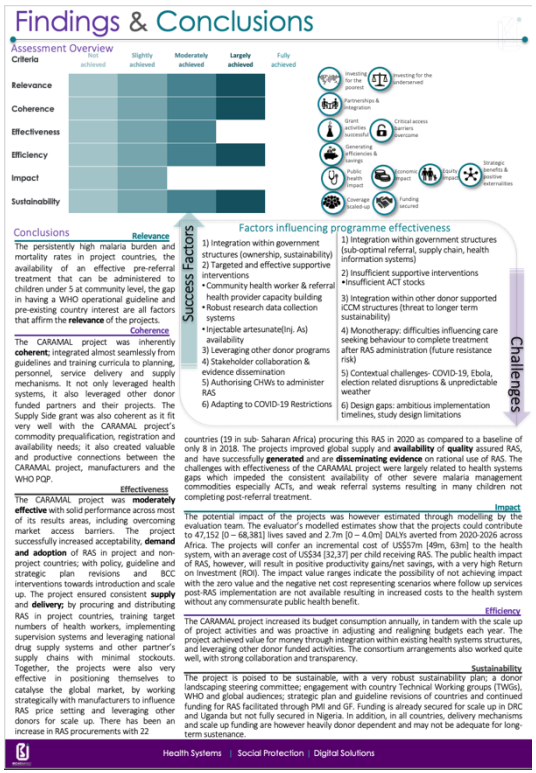
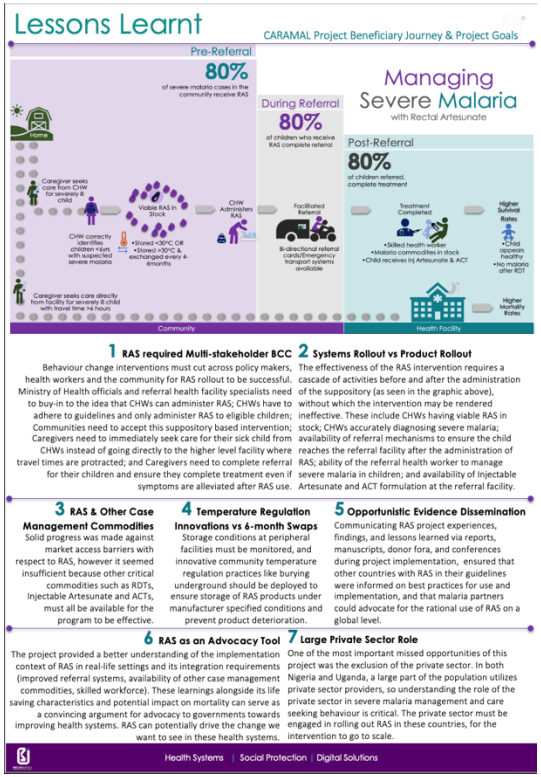
8 Appendices

8.1 4-Page Summary

see email attachment







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8.2 Human Angle Stories

I'm Now Equipped to Save Lives…VHT, Oyam District

Photo credit: BroadImpact

My name is Olang Francis. I am a VHT attached to Atipe HCIII and I come from a small village called Dogapwo in Oyam district.

I have worked on the ICCM program focusing on all three diseases malaria, pneumonia and diarrhoea for several years now.

My role on the CARAMAL project is to ensure that all children under 5 years with danger signs of complicated malaria get treatment. As a VHT, I also ensure that there is a linkage between the community and the health facility.

Before Rectal Artesunate (RAS) was available, we only referred severe malaria cases, *and some children die during the referral process.* With the introduction of RAS, we were trained on how to administer it as a pre referral treatment.

RAS is important because it stabilizes the child enough to travel to the referral facility. The only challenge is the long distance to facilities and ensuring the client gets there; especially because some clients are very weak.

One of the many clients I have served in the past three years, was a grandmother with a sick three year old grandchild. The child had been vomiting for two days and had no appetite. Upon confirming malaria using RDT, I administered RAS and referred the child to the nearest health facility. The grandmother said to me *'without your help with the RAS, my granddaughter would have died because I stay alone with no support and am very poor'.*

RAS has lowered severe malaria deaths in my community!

Uganda

Fast-Track Care in Kole District


Photo credit: BroadImpact

My name is Akullo Rabecca from Alubi Village in Kole district.

It was an ordinary morning in May 2020 when we woke up to do our daily activities. Little did I know that my daughter had not been feeling well throughout the previous night. That morning, I noticed that my child was feeling very weak. She was convulsing and burning up with a fever so I took her to the VHT.

The VHT asked me about the signs my child showed which turned out to be complicated malaria.

The VHT gave my child Rectal Artesunate and referred me to Aboke Health Centre. When the VHT inserted the RAS, my daughter felt better immediately and *with the referral forms from the VHT, it became very easy because I was helped immediately at the facility.*

I really thank the VHT because if not for the RAS, my daughter would have had the continuous convulsions which scared me. The RAS intervention should please continue within the community because if this happened again, I would still get my child RAS from the VHTs.

I wish to appreciate the CARAMAL Project for considering our district !

Uganda

Communities Embrace Rectal Artesunate in Kenge District


Photo credit: BroadImpact

My name is Anaclet, I have been a CHWs coordinator, and a Health Centre Committee (HCC) president in BECECO Health Zone for about 7 years now. In my capacity as the HCC president I was involved in advocacy and sensitization activities on the CARAMAL project.

Our sensitization approaches increased demand of RAS through introducing RAS specific information in all our existing activities such as preschool consultations, immunization campaigns, radio talks, church programs and FGDs with community members. *The fact that the young children could receive care from right within their communities and through people they knew and trusted was a source of satisfaction in itself from the big majority of community members.*

As the uptake of RAS continued to steadily increase, we witnessed very positive reactions from the community.

In many instances, children who presented with danger signs of severe malaria saw their condition dramatically improve minutes after RAS administration. They stopped convulsing, they were able to feed again, they were saved from dying right in the hands of their caretakers before they were referred to a higher-level facility for continued care. *We experienced a reduction in funerals related to under 5 mortality in our communities across the intervention districts.*

The response to RAS administration was so fast that community members referred to it as *"Intervention Rapide",* a term borrowed from the special police unit trained to provide timely response to crime. This quick response also had the dual effect of some parents not seeing the need to complete referral as most of the referral facilities were at least 8 km away, posing a monotherapy and future resistance risk. CHWs were able to identify these parents and provide follow up sensitization on the benefits of referral completion.

Our message to the funders and facilitators of the CARAMAL Project, is primarily one of gratitude. Our communities have ripped the true benefits of reduced mortality among our young children.

DRC

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8.3 Public Health & Economic Impact Model Methodology

The Impact Modelling was designed to estimate the direct and indirect impacts of the CARAMAL project. Since many countries are already procuring or planning to procure RAS doses, the impact of CARAMAL was not limited to the strict use of RAS, but the supporting interventions along the continuum of care. It is the interventions that provide the differentiating element in RAS program implementation so the methodology developed to estimate the impact focused on how those supportive structures would have influenced specific indicators in the model, e.g. treatment administration and case fatality rates.

8.3.1 Methodology

Two scenarios were developed to model the differences between the CARAMAL project impact on RAS implementation in a real-world situation versus alternative circumstances in which a country implements the use of RAS without the key supporting interventions which the project provided. These two scenarios are the Impact Scenario and the Counterfactual Scenario. The Impact Scenario models the multi-step process of severe malaria patients through the care system as was documented in the study protocols. Some of the study results were leveraged as inputs for specific calculations. These instances are outlined in the following methodological documentation. The Counterfactual Scenario takes a simplified approach and distils the multi-step approach from the Impact Scenario down to three fundamental utilizations of RAS within the care system: optimal use, suboptimal use, and no use. Although the Counterfactual is only hypothesized, it also leverages the data inputs from the Impact Scenario in order to strengthen the impact assumptions. In each scenario, the modelled fatalities are counted and the difference between the scenario fatalities is the measure of the impact.

The scenarios begin in 2020 and the model forecasts out to 2026. The indicator data used in 2020 aligns with the post-RAS period data collected from the project study by Swiss TPH. After 2020, certain indicators increase or decrease to reach estimated goals or targets by the end of the forecast. The starting population for all scenarios is the *number of children <5 with severe malaria reached by a RAS program area who consult a CHW and/or peripheral health facility*. This population is derived starting from the general population size, reduced by the proportion of the population served by CHW or peripheral health facility, reduced again by the reach of the RAS program, and then final an estimate of the incidence of severe malaria.

8.3.1a Impact Scenario

The Impact Scenario was designed to capture the major decision nodes along the continuum of care for a severe malaria patient. Because RAS is a pre-referral intervention, it's optimal use is contingent on patients completing referrals and receiving further treatments. The decision tree begins with children <5 with severe malaria visiting a community health worker (CHW) or peripheral health facility and the outcome of the tree is to tally the number of fatalities, given the treatment administration along the way (see image 8.3.1.1).

The four key treatment decision nodes in the algorithm tree are:

1. Patient receives RAS (or does not)
2. Patient completes referral (or does not)
3. Patient receives injectable Artesunate (or does not)
4. Patient receives ACT (or does not)

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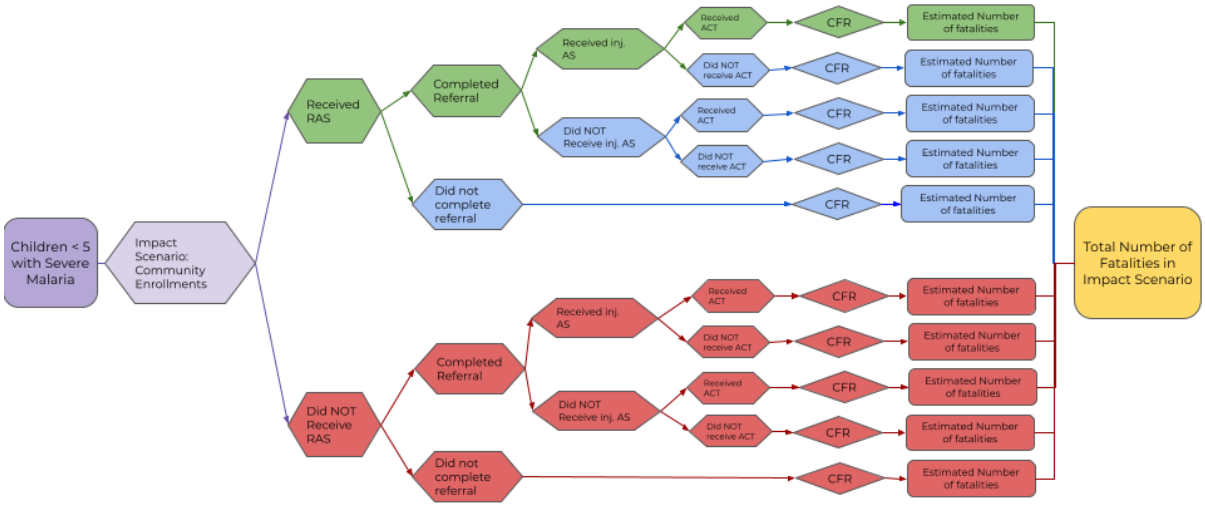
Image 8.3.1.1 Impact Scenario treatment algorithm



The hypothesis is that patients who receive RAS from the CHW, who then complete referral and receive additional treatments for severe malaria (inj. AS and ACT) will have lower fatality rates than patients who do not receive RAS and/or do not complete referrals or receive further treatments. Preliminary results from the project did not strictly support this hypothesis but additional analysis to control for confounding variables is still being researched. Despite these deviations, the study results were honoured through the inputs in order to reflect the variance of the real-world dynamics that were observed in each country.

Within the Impact Scenario, there are also three use cases to model a range of inputs/results: moderate case, worst case, and best case. All use cases begin with the same assumptions for the first two years, 2020-2021 and then diverge thereafter. For those two years, the input data reflects what was observed from the project implementation.

- Moderate Use Case – from 2022-2026, the study result input data assumes improvement is made for all indicators including RAS use, referral completion rates, other treatment administration rates, and case fatality rates (CFR). RAS, referrals, and treatment rates increase over the forecast whereas case fatality rates decrease to expected levels for patients receiving proper treatment. The increases/decreases are implemented on a linear basis between 2022 and 2026.
- Worst Use Case – from 2022-2026, the study result input data is held constant in all years. No improvement to treatment rates or CFRs is modelled in this use case.
- Best Use Case – this use case assumes a greater vector of improvement for all indicators than was modelled in the moderate use case. For RAS use, referral completion rates, and other treatment rates, the best use case assumes a 2026 result that is 5% higher than the result achieved by the moderate use case in the same year.

8.3.1.b Counterfactual Scenario

The Counterfactual Scenario is a simplified version of the algorithm tree used in the Impact Scenario. The decision nodes illustrated in image 8.3.1.1 were categorized into three uses of RAS:

1. Optimal Use (green shapes in image 8.3.1.1) – a patient is correctly diagnosed by the CHW and receives RAS. The patient then completes referral at a facility where they receive injectable Artesunate and ACT.
2. Suboptimal Use (blue shapes in image 8.3.1.1) – a patient is correctly diagnosed by the CHW and receives RAS but then the patient doesn't complete referral or even after completing referral, they do not receive one or both treatment of inj. AS and ACT.

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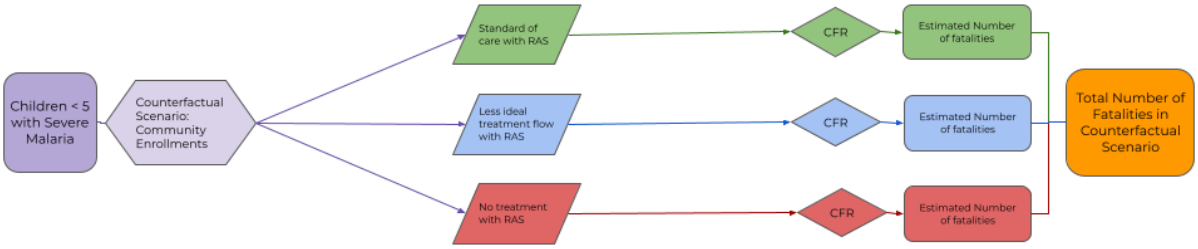
3. No Use (red shapes in image 8.3.1.1) – a patient is incorrectly diagnosed by the CHW and does not receive RAS. The patient may or may not complete referral or receive additional treatments.

Image 8.1.4.2 illustrates the three uses of RAS that were utilized for the Counterfactual.

The inputs used in the model for this scenario are averages or other derivatives of the data used for the Impact Scenario. The basis for this counterfactual is that the country did procure and distribute RAS doses but the program does not benefit from the supporting interventions around referral systems and iCCM that were implemented via the CARAMAL project. This scenario assumes that fewer patients experience the optimal use of RAS care track than is observed in the Impact Scenario.

Image 8.3.1.2 Counterfactual Scenario treatment algorithm



8.3.1.c Scale-Up Calculation

In order to scale the impact estimates to additional countries, global malaria burden estimates were refined by various proportions to obtain the number of children <5 with severe malaria who could receive RAS. Steps used to calculate the scale-up:

1. Obtain the estimated number of malaria cases attributed to African countries (the focus region for the scale-up in this model) from the World Malaria Report.
2. Multiply (1) by the estimated proportion of malaria cases that are children <5.
3. Multiply (2) by the estimated proportion of African countries that adopt RAS to obtain the estimated number of malaria cases among children <5 who live in a country with RAS.
4. Multiply (3) by the suspected incidence of severe malaria in children <5.
5. Multiply (4) by the estimated proportion of a country's population that seeks care from a CHW or peripheral health facility to obtain the estimated number of children <5 with severe malaria who visit a facility that would provide RAS.
6. Multiply (5) by the estimated proportion of the population that is covered by a RAS program (increases annually in the model) to obtain the number of children <5 with severe malaria who could be given RAS.

The result of the 6 steps above is the number of RAS doses administered in the scale-up countries. The estimated Number of Lives Saved is calculated by using the average ratio from the project countries for *Estimated number of Lives Saved per RAS dose administered*. By multiplying these two values, we obtain the estimated number of Lives Saved across all scale-up countries in the Africa Region.

To calculate the DALYs in the scale-up scenario, the average ratio for *Estimated fatalities among children <5 with severe malaria who consult a CHW per Life Saved* is calculated from the project countries and applied to the Lives Saved in the scale-up. The additional impact indicators can now be calculated using the Lives Saved and Fatalities applicable to the scale-up countries.

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8.4 Participants List

Global Participants

S/No	Organization/Participant Type	Job Title	Names
1	Unitaid Directors	Director, Strategy	Janet Ginnard
2	Unitaid Directors	Director, Programme Management	Robert Matiru
3	Unitaid Directors	Director, Results Team	Vincent Bretin
4	Unitaid Project Staff	CARAMAL Program Manager	Ambachew Yohannes
5	Unitaid Project Staff	Monitoring and Evaluation Manager	Ombeni Mwerinde
6	Unitaid Project Staff	PSM Manager	Ademola Osigbesan
7	Unitaid Project Staff	Technical Manager Strategic Sourcing and Supply	Kenny Onasanya
8	Unitaid Project Staff	Senior Finance Manager	Ganesh Ramachandran
9	Unitaid Project Staff	Technical Officer	Dale Halliday
10	Lead grantee – CHAI	Vice President for Global Malaria	Justin Cohen
11	Lead grantee – CHAI	Director of Operations	Jessica Fast
12	Lead grantee – CHAI	CARAMAL Technical Lead	Theodoor Visser
13	Lead grantee – CHAI	Community Health Manager	Harriet Napier
14	Lead grantee – MMV	Senior Director, Market Dynamics and Global Access Partnerships	Pierre Hugo
15	Lead grantee – MMV	Associate Director, External Relations, Corporate Affairs	Olaug Bergseth
16	Lead grantee – MMV	Director, Access & Product Management	Hans Rietveld
17	Lead grantee – MMV	Social Research Manager, Access & Product Management	Maud Majeres Lugand
18	Consortium partner – Swiss TPH	Co-PI / Head Medicines Implementation Research Unit	Christian Burri
19	Consortium partner – Swiss TPH	Co-PI / Head of Unit	Chirstian Lengeler
20	Consortium partner – Swiss TPH	CARAMAL DRC Lead	Aita Signorell
21	Consortium partner – Swiss TPH	CARAMAL Uganda and Nigeria Lead	Manuel Hetzel

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22	Consortium partner – Swiss TPH	Health Economist	Mark Lambiris
23	Consortium partner – UNICEF	Global Malaria and Partnerships Advisor & CARAMAL focal point	Valentina Buj
24	World Health Organization	Technical Officer, Global Malaria Programme	Silvia Schwarte
25	Global Fund	Senior Malaria Advisor	Roopal Patel
26	President's Malaria Initiative (PMI)	Africa Regional Malaria Advisor	Jordan Burns
27	Bill & Melinda Gates Foundation (BMGF)	Program Officer	Abigail Pratt
28	PSI	Malaria Technical Advisor	Keith Esch
29	Manufacturer-Tridem (owned by Fosun)	President	Lily Su
30	Manufacturer- Strides	Ass VP Marketing	Vinod Nair

Country Level Participants

S/No	Country	Organization/Participant Type	Title	Names
1	DRC	Lead grantee – CHAI	Program Manager	Dr. Fatou Mwaluke
2	DRC	Lead grantee – CHAI	Malaria Associate CARAMAL	Jenny Bokanga
3	DRC	Consortium partner – UNICEF	Manager Unite SMNEA et RSS	Lydia Mulongo Kabamba
4	DRC	Malaria TWG	Responsible de la prise en charge	Dr. Francois Mwema
5	DRC	NMCP	Point Focal CARAMAL PNLP/NMCP	Dr. Jean Claude Tembele
6	DRC	WHO	Cluster Coordinator/Communicable Diseases	Dr. Bacary Sambou
7	DRC	PMI/USAID	Deputy Coordinator	Mr. Tshiswaka
8	DRC	Global Fund Country Coordinating Mechanism (CCM)	Permanent Secretary	Pepe Kilimalima Ngwasi
9	DRC	Global Fund Principal Recipient	Project Manager	Fernandine Phanzu
10	DRC	Global Fund Sub-Recipient	Focal Point FDSS Kwilu	Mathieu Lunula
11	DRC	Research partner – Kinshasa School of Public Health (KSPH)	Sub Investigator	Prof. Antoinette Tshefu
12	DRC	Health Zone MoH-KINGANDU	Médecin Chef de Zone	Willy Kuziena
13	DRC	Health Zone MoH-KINGANDU	Malaria Focal Point Person	Voska Malakou
14	DRC	Health Zone MoH- KENGE	Médecin Chef de Zone	Leon Makambu

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15	DRC	Health Zone MoH- KENGE	Malaria Focal Point Person	Jean Bosco Manima
16	DRC	Community Group Representative- KENGE	Coordonnateur des relais communautaires	Anaclet Mbemba
17	DRC	Clinician -Kingandu	Infirmier Titulaire – CS CBCO	AG Rolande Sindani
18	DRC	Clinician – Kenge	Infirmier Titulaire -CS MAKIALA	Jean Rene Makambu
19	DRC	Commodity Logistics Manager	Pharmacien – Centrale de Distribution	Alexis Nkila
20	DRC	Commodity Logistics Manager	Pharmacien- Bureau Central Kenge	Lebon Mvuzi
21	DRC	Community Health Facility Worker	Relai communautaire KENGE	Kakesa Donatien
22	Nigeria	Lead grantee – CHAI	Deputy Director	Dr. Chizoba Fashanu
23	Nigeria	Consortium partner – UNICEF	Field Programme Officer	Mr. Oluseyi Olusunde
24	Nigeria	Consortium partner – UNICEF	Field Programme Officer	Dr. Emmanuel Emedo
25	Nigeria	Ministry of Health	Child Health/iCCM Desk Officer	Dr. Oluseyi Omokore
26	Nigeria	Ministry of Health, Malaria TWG	Head, Case Management	Dr. Nnenna Ogbulafor
27	Nigeria	Ministry of Health, NMEP	Case Management Desk Officer	Dr. Emmanuel Shekaru
28	Nigeria	Research partner – Akena	Associate Director	Dr. Elizabeth Omoluabi
29	Nigeria	State Level MoH/Malaria Program- Adamawa State	State Malaria Programme Manager	Mr. Benjamin Nashon Gubi
30	Nigeria	LGA Level MoH/Malaria Program- Fufore	LGA Malaria Focal Person	Mr. Yahya Ibn Said
31	Nigeria	LGA Level MoH/Malaria Program- Mayo Bela	LGA Malaria Focal Person	Mr. Hayatu Usman
32	Nigeria	LGA Level MoH/Malaria Program- Song	LGA Malaria Focal Person	Haj. Hauwa Nasara
33	Nigeria	Clinician Mayo Belwa	PMO	Dr. Peter Pwaspo
34	Nigeria	Clinician Fufore	PMO	Dr Aji Aliyu
35	Nigeria	Clinician Song LGA	Nurse	Ms Safia Bedan
36	Nigeria	LGA Logistics Manager Fufore	LGA Logistics Manager	Mrs Peace Audu
37	Nigeria	LGA Logistics Manager Mayo	LGA Logistics Manager	Mrs Fadimatu

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		Belwa		Hammanjoda
38	Nigeria	LGA Logistics Manager Song	LGA Logistics Manager	Mr. Alfred Gabriel
39	Nigeria	Community Group Representative	WDC Fufore	Jauro Hamman-gare
40	Nigeria	Community Group Representative	WDC Mayo Belwa	Alh Hammanjoda Ali
41	Nigeria	Community Health Facility Worker Mayo Belwa	Community Health Facility Worker	Halima Abubakar
42	Nigeria	Community Health Facility Worker Fufore	Community Health Facility Worker	Pwanogosi Emmanuel
43	Nigeria	Community Health Facility Worker Song	Community Health Facility Worker	Alfred Musa
44	Nigeria	State Logistics Manager	State Logistics Manager	Mr. Bala Lotan
45	Nigeria	CSO	Chairman NURTW	Mr. Jibril Njiidda
46	Nigeria	Global Fund	Disease Fund Manager – Nigeria Malaria	Jo-Angeline Kalambo
47	Uganda	Lead grantee – CHAI	Program Manager -Malaria	Alex Ogwal
48	Uganda	Consortium partner - UNICEF	Health Specialist	Dr. Fred Kagwire
49	Uganda	Ministry of Health	ICCM Focal Person	Dr. Maureen Amutuhaire
50	Uganda	Ministry of Health	Case Management Focal Person	Dr. Denis Rubahika
51	Uganda	Research Partner - Makerere University	CARAMAL Study PI	Dr. Phillis Awor
52	Uganda	District Level MOH/Malaria Program - Kole	Malaria Focal Person -Kole	Opito Samuel
53	Uganda	District Level MOH/Malaria Program -Oyam	Malaria Focal Person -Oyam	Oming Lamech
54	Uganda	Community Group Representative	Village health Teams - Kole	Atiino Doris
55	Uganda	Community Group Representative	Village Health Teams - Kole	Ameny Godfrey
56	Uganda	Community Group Representative	Village Health Teams - Oyam	Okot Abel
57	Uganda	Community Group Representative	Village Health Teams - Oyam	Okello Jimmy Smart
58	Uganda	Community Group	Village Health Teams - Oyam	Olang Francis

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		Representative		
59	Uganda	Clinician	Senior Clinical Officer - Kole	Okecha John Samuel
60	Uganda	Clinician	Senior Clinical Officer - Oyam	Ayo Denis
61	Uganda	Commodity Logistics Manager	Stores and logistics Officer - Kole	Apio Stella
62	Uganda	Commodity Logistics Manager	Clinical Officer/Logistics officer	Olal Lamech

8.5 Interview/Group Discussion Guides

These guides have been tailored to contain only information relevant to the different stakeholder types as well as questions not exhaustively answered from the available project documentation. Nine guides have been developed they include:

1. Donors & Global Stakeholders interview/discussion guide

CARAMALSS KII Guide- Donors &

2. Manufacturers' interview/discussion guide

CARAMALSS KII Guide-

3. Grantees & Consortium Members interview/discussion guide

CARAMALSS KII Guide- Unitaid,

4. Research Partners (Swiss TPH and Other In-country Partners) interview/discussion guide

CARAMALSS KII Guide- Research

5. Ministry of Health/NMCP (National Level) interview/discussion guide

CARAMALSS KII Guide- MoH

6. Ministry of Health/NMCP (Sub-national level) interview/discussion guide

CARAMALSS KII Guide- MoH Sub-

7. CSO interview/discussion guide

CARAMALSS KII Guide- CSOs.docx

8. Health Workers interview/discussion guide (Commodity Logistics Managers, Clinicians at Referral Facility and Community Health Workers/Health Workers at Peripheral Health Facility)

CARAMALSS KII Guide- Health

9. Community Groups interview/discussion guide

CARAMALSS KII Guide- Community

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