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Expanded Retrospective:

Rectal Artesunate

This retrospective was developed to inform *Discerning Demand: A Guide to Scale-Driven Product Development and Introduction*, a publication developed by the Center for Innovation and Impact, USAID that explores how global health practitioners (including funders, investors, innovators, implementing partners, etc) can better account for actual demand of new products. This retrospective is an in-depth historical analysis of how demand for this product was understood by different stakeholders supporting its development and introduction. The insights generated from this retrospective informed the recommendations in the full report.

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Expanded Retrospective: Rectal Artesunate (RAS)

1. Introduction

1.1. Product Summary

Rectal artesunate (RAS) is a pre-referral treatment for severe *P. falciparum* malaria in children under age six. It is recommended when the child is incapacitated due to severe malaria and where injectable artesunate is not readily available. After RAS is administered, children should be immediately referred to a facility where they can receive treatment with injectable artesunate and a three-day course of artemisinin-based combination therapy (ACT).¹

1.2. Fast Facts

Fast Facts (Note: sources noted in retrospectives)	 Rectal artesunate (RAS)
 Health Area	Severe malaria
 Market Archetype	Generic/commodity – not crowded market
 CII Global Health Innovation Index	Incremental
 Expected Buyers/Procurers	PMI, MMV & GFATM, some country funding
 Funders	Studies funded by WHO & Unitaid
 Countries	Registered in 20 countries, all in Africa
 Manufacturers	Strides Pharma & Cipla (both Prequalified)
 Intended Delivery Setting	Remote/rural care sites; CHWs; lower-level sites without access to parenteral artesunate
 Cost	<\$1 per suppository
 Uptake	~2-3M suppositories annually; dependent on donor commitments & WHO guidance

Fast fact source: CII Innovation Index,² Countries,³ Cost,⁴ Uptake.⁵

1 World Health Organization (2015). [Guidelines for the treatment of malaria.](#)

2 USAID Center for Innovation & Impact. [Global Health Innovation Index – A tool for identifying the most promising Global Health Innovations.](#)

3 Medicines for Malaria Venture. [Countries where artesunate rectal capsules is registered.](#)

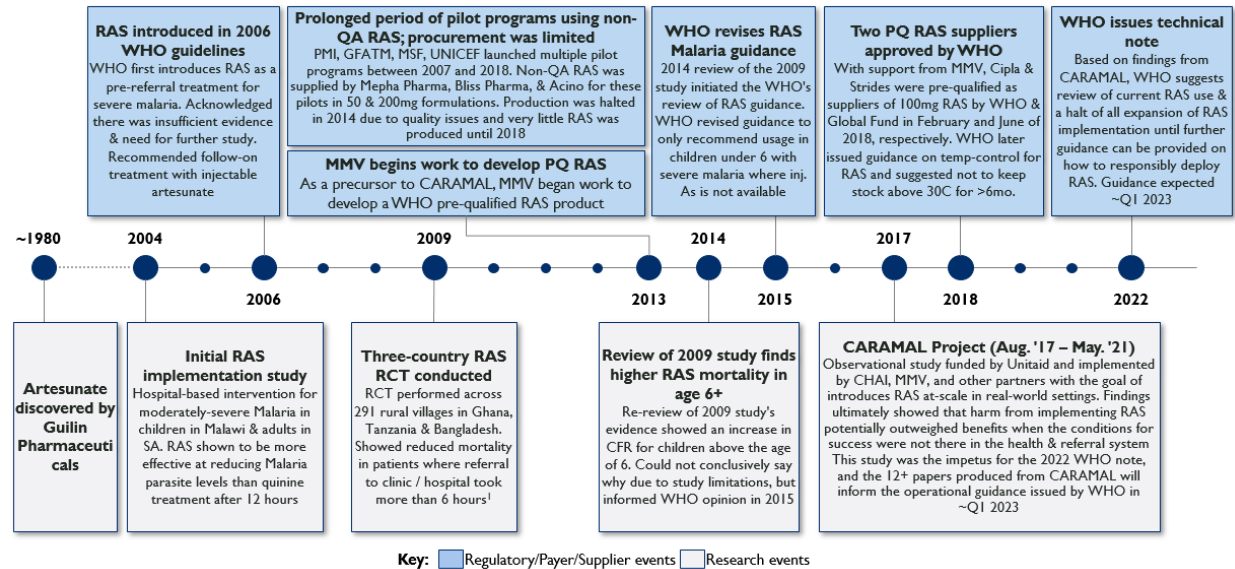
4 Unitaid (2018). [Rectal Artesunate Landscaping Assessment Report.](#)

5 Medicines for Malaria Venture (2022). [Severe Malaria Global Stakeholder Meeting 2022 report.](#)

2. Demand Story

2.1. Product Development Timeline

RAS | Product development timeline



1 Noting published limitations of this study by [Hirji, K, Trials, 2011](#).

2.2. Development

For children under age six with severe malaria, the risk of death is greatest in the first 24 hours. In rural settings, many children die from severe malaria due to long travel times to reach care at health facilities. Rectal artesunate is intended to fill this gap and prolong the life of children until they can receive injectable artesunate followed by a three-day course of artemisinin combination therapy (ACTs). Rectal artesunate was first developed in the 1980s and was initially tested against quinine (the existing therapy) for efficacy in 2004.⁶ In 2006, RAS was recommended by the WHO for pre-referral treatment of severe malaria in remote areas when injectable artesunate is not available.⁷

2.3. Pilot Phase

After the WHO's recommendation in 2006, multiple studies looked further into the efficacy of RAS in the field. A 2009 RCT found RAS to significantly reduce mortality and morbidity from severe malaria for children arriving at the clinic at least six hours after the delivery of RAS. Within six hours, RAS was not found to have any effect.⁸ Although these statements have informed WHO guidance, they have also been refuted.⁹ These results were reviewed in 2014 and challenged for children above the age of six. In this age group, it was found that RAS had the opposite impact, increasing negative outcomes.¹⁰ In response, the WHO changed its guidance in 2015 to only recommend RAS for children under age six with severe malaria who live over six hours away from a referral facility.¹¹

Meanwhile, many countries were procuring non-prequalified RAS for introduction and scale-up as early as 2009. These efforts occurred across more than 20 countries and over four million suppositories were procured from 2009 to 2017 as part of these efforts.¹²

6 Barnes, et al. (2004). Efficacy of rectal artesunate compared with parenteral quinine in initial treatment of moderately severe malaria in African children and adults: a randomised study.

7 World Health Organization (2006). Guidelines for the treatment of malaria.

8 Gomes, et al. (2009). Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial.

9 Hirji and Premji (2011). Pre-referral rectal artesunate in severe malaria: flawed trial.

10 Okebe, et al. (2014). Pre-referral rectal artesunate for severe malaria.

11 World Health Organization (2015). Guidelines for the treatment of malaria.

12 Unitaid (2018). Rectal Artesunate Landscaping Assessment Report.

2.4. Challenges Emerged

- **Incomplete referrals from communities to facilities** that were driven by (i) caregivers misinterpreting the interim recovery of RAS patients as a sign further care was not needed; (ii) barriers in transportation to and awareness of facilities for further care; (iii) inconsistent quality of care at higher-level care facilities, for example, stock outs of injectable artesunate⁷
- **Insufficient training of health workers** across levels of care on when to administer RAS and how to dose it. This was exacerbated in situations where RAS was not built into integrated Community Case Management or other community-based trainings.
- **Difficulties of forecasting, supplying, and storing RAS.** Countries struggled with RAS quantification due to RAS's niche use case and inconsistent data availability on the number of malaria cases in remote settings as well as patient journeys across health system levels. Because RAS was a new product, there was also no historical consumption data to guide forecasts. Storage conditions at community levels often exposed RAS to temperatures above 30 degrees Celsius, potentially leading to product deterioration after prolonged stock periods. While some product expiry was expected, there were few mechanisms in place to monitor and remove RAS that had deteriorated due to the heat.¹³

Acknowledging these challenges, global donors began to try to demonstrate the efficacy of RAS in the field and to understand how these challenges may be overcome. A study conducted in Zambia between 2017 and 2018 demonstrated RAS to be successful at reducing mortality of severe malaria when combined with health system changes such as training, emergency transport services, and quality of care at referral sites.¹⁴ However, to generate implementation guidance, RAS needed to demonstrate success in the hard-to-reach, community-based settings where it is expected to have the most impact. To this end, Unitaid launched the CARAMAL project in 2017.

Focusing on Nigeria, Uganda, and the DRC, Unitaid brought together a collaboration between MMV (to secure WHO prequalified supply), CHAI (to manage the project), UNICEF (to integrate in existing community health systems), and Swiss TPH (to evaluate impact). The collaboration started in 2017 with the goal of delivering guidance on how to effectively operationalize RAS in the field in order to overcome the known challenges.

As a precursor for the CARAMAL implementation study, a RAS product had to be prequalified by the WHO. Without WHO prequalification, Unitaid could not support RAS procurement. Unitaid supported MMV to identify two suppliers for prequalified product in 2018: Strides Pharma and Cipla Pharmaceutical. Shortly thereafter, CARAMAL began and ran from 2018 until May 2021.¹⁵

The CARAMAL study successfully generated significant evidence on care and treatment for children in hard-to-reach communities across three different community health system settings, culminating in more than 12 papers to inform operational guidance. The study also showed that when RAS is implemented in complex conditions, the product may cause more harm than benefit, raising alarm.¹⁶

After the results of the CARAMAL project were released in May 2021, the WHO recommended countries review the conditions of current RAS use and halt further expansion of RAS implementation until the WHO can provide further technical guidance on how to responsibly deploy RAS.¹⁷

¹³ Unitaid (2018). [Rectal Artesunate Landscaping Assessment Report](#).

¹⁴ Green, et al (2019). [Use of rectal artesunate for severe malaria at the community level, Zambia](#).

¹⁵ Unitaid (May 2021). [End-of-Grant Evaluation Report: Community Access to Rectal Artesunate for Malaria \(CARAMAL\) Project and Output 3 of the Supply Side Grant](#).

¹⁶ Unitaid (May 2021). [End-of-Grant Evaluation Report: Community Access to Rectal Artesunate for Malaria \(CARAMAL\) Project and Output 3 of the Supply Side Grant](#).

¹⁷ World Health Organization (2022). [The use of rectal artesunate as a pre-referral treatment for severe P. falciparum malaria: information note](#); Medicines for Malaria Venture (2022). [Severe Malaria Global Stakeholder Meeting 2022 report](#).

3. Learnings

Four key learnings from the demand story:

1. Limited acknowledgement of health system limitations

Recall the challenge: Early pilots on RAS did not assess health system readiness despite evidence that RAS was effective in the context of a system that was able to ensure referrals, transportation, and quality of care at referral sites. RAS is entirely dependent on a continuum of care that is a function of the health system. Countries were procuring RAS before it was prequalified, yet there were no studies that assessed the effectiveness of RAS introduction. CARAMAL demonstrated the challenges with implementing RAS in hard-to-reach, community-based settings.¹⁸

Forward-looking learning: As soon as recommendations are made for products with clear dependencies on other health system attributes, it is worth investing in implementation studies that focus on operational limitations (or enablers) sooner than later to inform policy and decision-making. Donors and advocates should assess the minimal viable environment required to ensure the product works accordingly.

2. Limited understanding and acknowledgement of the true current state of community health systems in low resource settings

Recall the challenge: The RAS patient journey depends on strong community health systems that enable CHWs, caregivers, and patients to navigate a multi-step and multi-setting process to properly diagnose severe malaria, administer a correct RAS dosage, and complete follow-on referral care in a health center. Community health systems receive the least investment compared with other settings and are often unprepared to adopt new products without significant investments.

Forward-looking learning: For new interventions at the community level, like RAS, understand the current sophistication of community health systems. Acknowledge when they may not suffice or make investments to raise the standard of care so that the product can have the intended effect.

3. Overemphasis on solving supply-side barriers

Recall the challenge: Global health donors invested significant time and resources attaining prequalified RAS suppliers but spent limited time solving for health system barriers in the RAS patient journey. These efforts responded to gaps that were identified by the global community at that time. Although important, in most cases, addressing supply barriers alone was not increasing access. Supply of RAS was not listed as a key challenge in the multiple pilots conducted by countries in this period and there was a track record of country-led procurement.¹⁹

Forward-looking learning: Innovators and donors need to watch for the risk of underinvesting in overcoming demand-side and health system barriers.

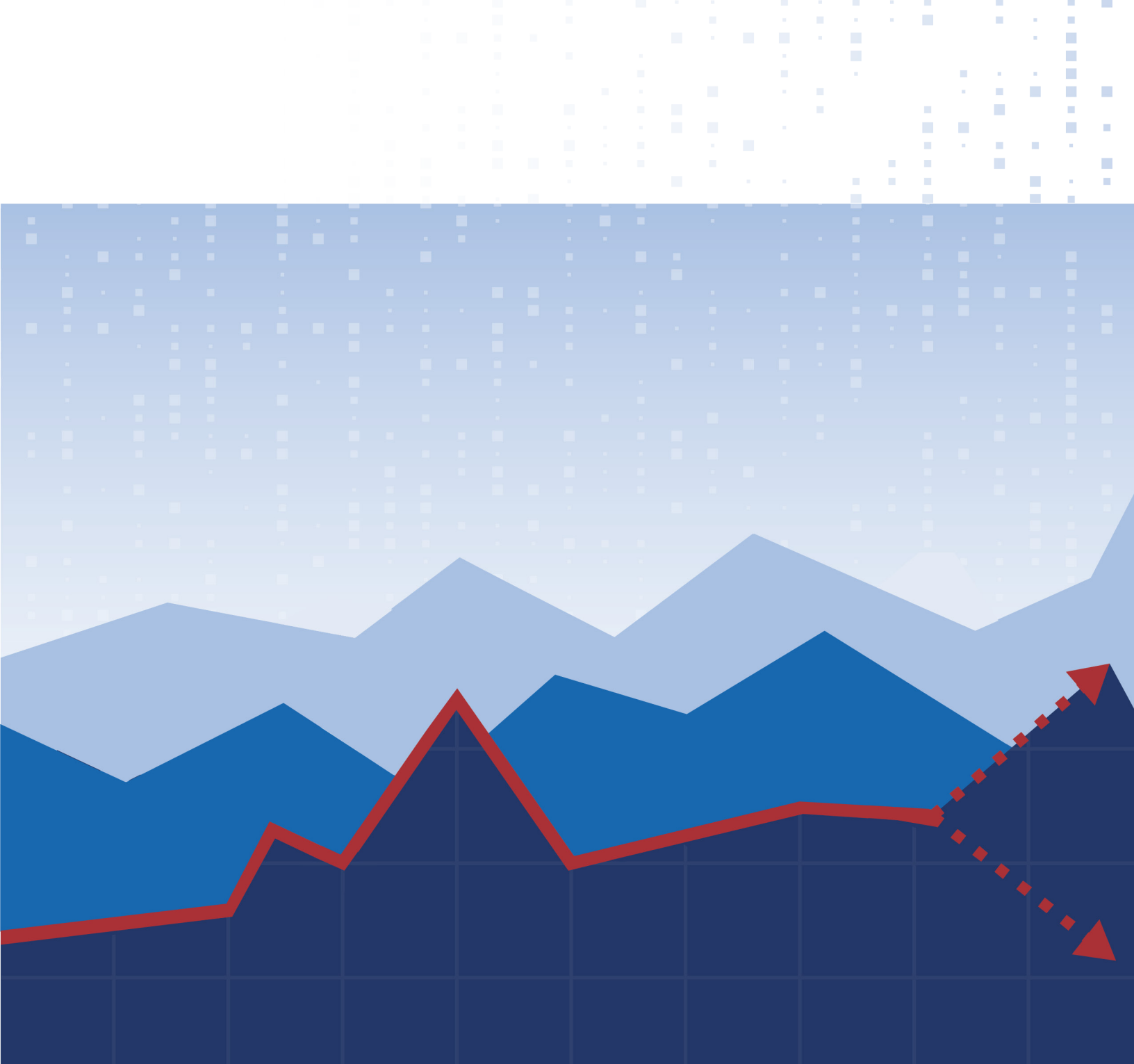
4. Acknowledge and account for uncertainty when forecasting for niche health products

Recall the challenge: Accurate forecasting of RAS demand can be complicated by a lack of reliable data on the target population (age six and under who live over six hours from a referral center); the availability, distribution, and capacity of community health workers; the unpredictability of severe malaria incidence; and poor data on RAS consumption. Forecasting is also compounded by difficulty of disentangling occurrence of severe malaria versus other severe febrile illnesses that commonly affect children in rural areas.

Forward-looking learning: Reducing uncertainty for niche products can occur through investments in data systems so that consumption, incidence, and patient care data can be monitored. Such data can be integrated into iterative forecasts that inform scenarios. Investments should prioritize data collection and use at the community level and ensure process and outcome indicators can be tracked across community- and referral-level care.

¹⁸ Non-Camaral countries such as Burkina Faso are now planning implementation studies with PMI support precisely for this reason.

¹⁹ Unitaid (2018). *Rectal Artesunate Landscaping Assessment Report*.



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