# Management of severe malaria: challenges and lessons learned with the introduction of pre-referral Rectal Artesunate in the Democratic Republic of the Congo

## INAUGURAL DISSERTATION

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## Table of contents

## List of tables

## List of figures

## List of acronyms

| | |
|---|---|
| 95% CI | : 95% Confidence Intervals |
| ACT | : Artemisinin-based Combination Therapies |
| AL | : Artemether-lumefantrine |
| AM | : Antimalarial |
| AMq | : Amodiaquine |
| Amoxi | : Amoxicillin |
| aOR | : Adjusted odds Ratios |
| AP | : Artesunate-pyronaridine |
| ART | : Artemether |
| AS | : Artesunate |
| AS-AQ | : Artesunate-amodiaquine |
| BCC | : Behavior Change Communication |
| CARAMAL | : Community Access to Rectal Artesunate for Malaria |
| CFR | : Case Fatality Ratio |
| CHAI | : Clinton Health Access Initiative |
| CHCS | : Community health care site |
| CHW | : Community Health Worker |
| COVID-19 | : Coronavirus disease 2019 |
| CRF | : Case report form |
| CU5 | : Children under 5 |
| DHA-PQ | : Dihydroartemisinin-piperaquine |
| DHS | : Demographic and Health Survey |
| DHS-DRC II | : DRC second Demographic and Health Survey |
| DRC | : The Democratic Republic of the Congo |
| g/dL | : Gram per deciliter |
| GDP | : Gross Domestic Product |
| GPS | : Global positioning system |
| HA | : Health Areas |
| Hb | : Haemoglobin |
| HF | : Health facility |
| HRP2 | : *Plasmodium falciparum* antigen histidine rich protein 2 |
| HSS | : Health system strengthening |
| HZ | : Health Zone |
| iCCM | : integrated Community Case Management |
| IMCI | : Integrated Management of Childhood Illness |
| IPTi | : Intermittent preventive treatment of malaria in infants |
| IPTp | : Intermittent preventive treatment in pregnancy |
| IPTsc | : Intermittent preventive treatment of malaria in school-aged children |
| IQR | : Interquartile Range |
| IRS | : Indoor Residual Spraying |
| ITT | : Intention-to-Treat |
| LGA | : Local Government Areas |

| | |
|---|---|
| LLIN | : Long Lasting Insecticidal Nets |
| M&E | : Monitoring and evaluation |
| MDA | : Mass drug administration |
| MICS | : Multiple Indicator Cluster Survey |
| MoH | : Ministry of Health |
| NA | : Not Applicable |
| NG | : Nigeria |
| NGO | : Non-Governmental Organizations |
| NMCP | : National Malaria Control Program |
| ODK | : Open Data Kit platform |
| OR | : Odds ratio |
| Parac | : Paracetamol |
| PCA | : Principal components analysis |
| PDMC | : Post-discharge malaria chemoprevention |
| PHC | : Primary health care facility |
| pLDH | : Plasmodium lactate dehydrogenase |
| PPE | : Personal protective equipment |
| PSS | : Patient Surveillance System |
| RAS | : Rectal Artesunate |
| RBC | : Red blood cells |
| RCT | : Randomized controlled trial |
| mRDT | : Malaria rapid diagnostic test |
| RHF | : Referral health facility |
| Rx | : Prescription |
| SD | : Standard deviation |
| SES | : Socioeconomic status |
| SM | : Severe Malaria |
| SMC | : Seasonal malaria chemoprevention |
| SP | : Sulfadoxine and pyrimethamine |
| STROBE | : Strengthening the Reporting of Observational Studies in Epidemiology |
| Swiss TPH | : Swiss Tropical and Public Health Institute |
| UG | : Uganda |
| UNICEF | : The United Nations Children's Fund |
| USA | : United States of America |
| WHO | : World Health Organization |

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## Summary

Malaria causes over 240 million cases and over 600,000 deaths annually, mostly among children under the age of five years. The Democratic Republic of the Congo (DRC) has the second highest malaria mortality in the world, accounting for 12% of the global burden of malaria. Despite substantial improvements in prevention and treatment during the past 10 years, malaria remains the principal cause of morbidity and mortality, accounting for 44% of all deaths among outpatient visits in children, and 22% of all in-patient deaths. One of the major challenges in severe malaria case management remains the limited access to higher-level health facilities where a full treatment can be provided. This is especially an issue for populations living in remote areas, resulting in treatment delays of several hours or even days. In such situations, the World Health Organization (WHO) recommends pre-referral treatment, either with a single dose of a parenteral anti-malarial, or with a single dose of rectal artesunate (RAS). The Congolese National Malaria Control Programme (NMCP) is committed to reducing the high number of malaria-related deaths through proven interventions such as pre-referral RAS. The aim of this thesis was to identify challenges and draw lessons learned from the implementation of pre-referral RAS in DRC, in view of supporting its responsible introduction into the national health system. The present work was entirely conducted in the frame of the multi-country Community Access to Rectal Artesunate for Malaria (CARAMAL) project.

In DRC, we setup a patient surveillance system (PSS) in three Health Zones to determine the distribution of dangers signs for severe malaria and assess their impact on RAS use, referral completion, injectable treatment and ACT provision, and health outcomes including death. To contextualize the data gathered through the PSS, we also conducted cross-sectional household surveys in the same locations to assess treatment seeking predictors and the prevalence of malaria.

Findings showed a high prevalence of malaria (45.1%, 95% CI 39.8–50.4) and anaemia (79.5%, 95% CI 77.1–81.7) in these communities. The presence of danger signs was not optimal but still increased the likelihood of seeking treatment (aOR=2.12, 95% CI 1.03–4.38). Unfortunately, still many children with danger signs were not brought to health facilities, or were brought late. Importantly, danger signs were well recognized by health provider at the primary care level, and RAS is acceptable and can be given without problem by low-level health care workers.

Referral Health Facilities (RHF) are the subsequent point of contact for severely ill children, after they successfully complete their referral.

According to the current treatment recommendations, the post-referral treatment of severe malaria comprises the provision of parenteral artesunate for at least 24 hours, followed by a full course of an Artemisinin Combination Therapy (ACT) once the patient can tolerate oral medication. In the RHFs, our aim was to assess the compliance of health care workers with the recommended treatment in children under 5 years. While only half of children were given parenteral antimalarial treatment (50.3%, 2,117/4,208), inpatient ACT administration was more common (78.7%, 1,314/1,669). The overall poor quality of severe malaria case management at higher-level facilities is an important health system issue and it is probably the reasons why the introduction of RAS did not have an impact on the Case Facility Rate of the pediatric patients. In addition, parenteral artesunate not followed up with oral ACT constitutes an artemisinin monotherapy and may favor the selection of resistant parasites. Stricter compliance with the WHO severe malaria treatment guidelines is critical to effectively manage this disease and further reduce child mortality.

Finally, we assessed the health system costs and constraints to the successful implementation of pre-referral RAS at community level. We did so to inform operational guidance and financial planning for the scale-up of RAS as pre-referral treatment for severe malaria. The equivalent annual costs of preparing the health system for managing severe malaria with RAS was $4.19 per child at risk, and $464 per child treated. Strengthening essential routine health system components accounted for the majority of these costs (76.4%).

In conclusion, introducing pre-referral RAS as a single intervention seemed not to add value in terms of reducing child mortality. Deploying successful pre-referral RAS at large scale requires preceding investments to strengthen the health system along the entire cascade of care. Only then can the potential of RAS as a pre-referral treatment be realized.

## Résumé

Le paludisme provoque plus de 240 millions de cas et 600.000 décès chaque année dans le monde, principalement chez les enfants de moins de cinq ans. La République démocratique du Congo (RDC) a le deuxième taux de mortalité lié au paludisme pour un total de 12% du fardeau mondial du paludisme. Malgré des améliorations substantielles dans la prévention et le traitement au cours des 10 dernières années, le paludisme reste la principale cause de morbidité et de mortalité, représentant 44% des décès parmi les consultations externes d'enfants de moins de 5 ans, et 22% des décès dans les structures sanitaires. L'un des principaux défis de la prise en charge des cas de paludisme grave reste l'accès limité aux structures de santé de niveau supérieur, en particulier pour les populations vivant dans des zones reculées. Ceci entraîne des retards de traitement de plusieurs heures, voire de plusieurs jours. Dans de telles situations, l'Organisation Mondiale de la Santé (OMS) recommande un traitement pré-référentiel, soit avec une dose unique d'un antipaludéen parentéral, soit avec une dose unique d'artésunate rectal (RAS). Le Programme national de lutte contre le paludisme (PNLP) s'est engagé à réduire le nombre élevé de décès liés au paludisme, en particulier chez les enfants de moins de 5 ans, grâce à des interventions éprouvées dont fait partie le traitement pré-référentiel avec le RAS. L'objectif principal de cette thèse était d'identifier les défis et de tirer les leçons de la mise en œuvre du RAS en pré-référence, afin de soutenir son introduction responsable dans le système de santé de la RDC. Cette étude a été réalisée entièrement dans le cadre de l'étude multicentrique *Community Access to Rectal Artesunate for Malaria* (CARAMAL).

En RDC, nous avons mis en place un système de surveillance des patients (PSS) dans trois zones de santé, afin de déterminer la distribution des signes de danger du paludisme grave et évaluer leur impact sur l'utilisation du RAS, l'aboutissement des références, le traitement parentéral, et finalement l'administration des CTA. Pour contextualiser les données recueillies par le PSS, nous avons également mené des enquêtes transversales auprès des ménages dans les mêmes sites, afin d'évaluer les prédicteurs de la recherche de traitement et de la prévalence du paludisme. Les résultats suggèrent que la reconnaissance des signes de paludisme grave par les gardiens était faible où la prévalence du paludisme (45.1%, 95%CI 39.8–50.4) et de l'anémie (79.5%, 95%CI 77.1–81.7) sont élevées. Toutefois, la présence de signes de danger augmentait la probabilité de demander un traitement (aOR=2.12, 95%CI 1.03–4.38), même si de nombreux enfants présentant des signes de danger n'étaient pas amenés dans les structures de santé, ou alors tardivement. Il est important de noter que les signes de danger ont été

raisonnablement bien reconnus par les prestataires de soins de santé au niveau des structures de santé primaires, que le RAS était acceptable et qu'il a été administré de manière adéquate.

Les structures de référence constituent le prochain point de contact pour les enfants gravement malades, et qui ont complété avec succès la référence. Selon les recommandations actuelles, le traitement post-référence du paludisme grave comprend l'administration d'artésunate par voie parentérale pendant au moins 24 heures, suivie d'un traitement complet par CTA lorsque le patient peut tolérer le médicament par voie orale. Alors que seulement la moitié des enfants ont reçu un traitement antipaludique parentéral (50.3%, 2,117/4,208), l'administration d'une CTA en milieu hospitalier était courante (78.7%, 1,314/1,669). Cela démontre malheureusement la relativement mauvaise qualité de la prise en charge du paludisme grave au niveau supérieur de soins, et cela mène à un mauvais impact du traitement précoce offert par le RAS au niveau communautaire. De plus, l'artésunate parentéral non suivi d'une CTA constitue une monothérapie à base d'artémisinine, qui peut favoriser la sélection de parasites résistants. Un respect plus strict des directives de l'OMS pour le traitement du paludisme grave est essentiel pour gérer efficacement cette maladie et réduire davantage la mortalité infantile.

Nous avons également travaillé sur les coûts et les contraintes à la mise en œuvre du RAS en pré-référence. L'objectif de cette partie était d'évaluer empiriquement les coûts réels de l'introduction à grande échelle du RAS au niveau communautaire, y compris le renforcement du système de santé de routine. Ceci dans le but de fournir des conseils fondés pour la mise à l'échelle du RAS comme traitement de pré-référence pour le paludisme grave. Le coût annuel de la préparation du système de santé à la prise en charge du paludisme était de $4,19 par enfant à risque, et de $464 par enfant traité en RDC. Le renforcement des autres composantes négligées du système de santé représentait la majorité de ces coûts, soit 76,4%. Les coûts spécifiques liés à l'introduction du RAS représentaient la minorité restante. La mise à l'échelle du RAS ou d'autres interventions reposant sur les prestataires de soins de santé communautaires n'a de sens que si elle s'accompagne d'investissements supplémentaires essentiels dans le système de santé, soutenus sur le long-terme.

En conclusion, le système de santé de la RDC a de nombreux défis à relever en matière de gestion du paludisme grave à tous les niveaux. L'introduction du RAS en pré-référence en tant qu'intervention unique ne semble pas apporter de valeur ajoutée en termes de réduction de la mortalité infantile. Le déploiement à grande échelle du RAS en pré-référence nécessite un investissement préalable dans le renforcement du système de santé le long de la cascade de soins, afin de déployer son effet protecteur.

# 1. Introduction

## 1.1. Malaria parasite biology and disease

### 1.1.1. Malaria parasite

Malaria is a parasitic mosquito-borne disease caused by an intraerythrocytic protozoan of the genus *Plasmodium*. Five *Plasmodium* species possess the ability to infect humans: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale,* and *Plasmodium knowlesi* (White *et al.* 2014, Buck *et al.* 2022, MMV 2022). Recently, *Plasmodium ovale* was recognized as two morphologically indistinguishable sympatric sub-species namely *P. ovale curtisi* (the classic type) and *P. ovale wallikeri* (Sutherland *et al.* 2010, Ashley *et al.* 2018, Milner 2018). It is established that *Plasmodium falciparum* and *P. vivax* are the predominant parasite species to humans worldwide. *Plasmodium falciparum* is the major cause of malaria-related morbidity and severe disease responsible of malaria mortality in tropical settings mostly in sub-Saharan Africa (Marsh *et al.* 1995, Ashley *et al.* 2018). Usually, *Plasmodium vivax* produces milder disease, but this parasite can also lead to severe disease, and recurrent episodes bring significant problems. *Plasmodium malariae* and both *Plasmodium ovale* species are understudied, but their severity of illness is likely to be closer to uncomplicated *P. vivax* disease. *Plasmodium knowlesi* known as a species of *Plasmodium* that primarily infects non-human primates, used to be often misdiagnosed by microcopy because of its likeness to *P. malariae*. It can cause severe disease in humans, and is encountered in South-East Asia and the Western Pacific regions (Singh *et al.* 2004, Cox-Singh *et al.* 2008, WHO 2019).

### 1.1.2. *Plasmodium* lifecycle

The malaria parasite is haploid during most of its complex life cycle that unfolds in two distinct stages: an asexual reproduction stage in the human host, and a sexual one in the female mosquito, the definitive host. Human malaria infection starts by a bite of an infected female *Anopheline* mosquito vector, resulting in the inoculation of microscopic motile parasites (*sporozoites*) into the human blood stream during a blood feed. Within an hour sporozoites invade liver cells (hepatocytes) and then multiply asexually in thousands of pre-erytrocytic schizonts (*merozoites*) through a process called pre-erytrocytic schizogony. In *P. vivax* and *P. ovale* infections, a proportion of sporozoites become dormant in hepatocytes, leading to *hypnozoites* who can cause relapses weeks, months or even years after the primary infection.

This property of both species causes “relapsing malaria” and contributes to the recurring transmission of the parasites (Schäfer *et al.* 2021, Zanghi *et al.* 2021, MMV 2022).

When hepatic schizont bursts, mature merozoites enter the bloodstream and rapidly invade red blood cells (RBCs). They then start an erytrocytic schizogony with a swift asexual replication of their haploid genome (mitosis) through the ring, trophozoite and schizont stages, leading to a relapse of merozoites that continue the cycle by invading other RBCs. After several cycles, a subpopulation of merozoites switches into longer-lived sexual forms, producing both male and female *gametocytes* that cause no infection, but are infective for mosquitoes via a blood meal (Trampuz *et al.* 2003, Rangel 2022).

In the mosquito midgut, both male and female gametes fuse (sexual reproduction) to form a diploid *zygote* that in turn became motile and elongated (*ookinete*), and passes through the gut wall and develops into an *oocyst*. Meiotic division of the *oocyst* releases sporozoites, which migrate to the salivary glands of the female *Anopheles* mosquito, ready to completing the lifecycle back to another human (Beier 1998, Ashley *et al.* 2018, CDC 2022, Guttery *et al.* 2022, MMV 2022).

### 1.1.3. Malaria disease

Clinical symptoms of malaria develop primarily once the erytrocytic cycle leads to a parasitaemia above 100 parasites/µl as a result of schizonts rupture, leading to a the massive destruction of infected erythrocytes and the accumulation of related toxic wastes and host immune response (Ashley *et al.* 2018). As an obligate intracellular parasite, its successful development is dependent on its human host to supply the required nutrients through several mechanisms (Su *et al.* 2020, Counihan *et al.* 2021). Incubation period ranges from 7 to 30 days, varying by parasite species (shorter with *P. falciparum*; longer with *P. malariae*). Thus, Malaria disease can be categorized as uncomplicated or severe. Symptoms of uncomplicated malaria are non-specific, and can include fever, chills, sweats, headaches, cough, nausea, vomiting, body aches, general malaise, occasionally diarrhoea and splenomegaly.

Severe malaria is usually caused by *P. falciparum* and, occurs when infections are complicated by serious organ failures leading to vital organ dysfunctions (Trivedi *et al.* 2022). The definition of severe malaria consists of clinical and laboratory criteria including cerebral malaria, which is associated with abnormal behavior, impairment of consciousness (coma), multiple seizures or other neurological abnormalities; respiratory distress (acidosis); prostration; shock; pulmonary oedema (radiological); abnormal bleeding; jaundice; repeated

vomiting; severe anaemia; hemoglobinuria; hypoglycaemia; acute kidney injury; hyperparasitemia (White *et al.* 2014, WHO 2014, White 2018, WHO 2022). Three major clinical presentations of severe malaria are associated with mortality including coma, respiratory distress (acidosis) and severe anaemia (Molyneux *et al.* 1989, English *et al.* 1996, von Seidlein *et al.* 2012). Many adults with severe malaria also present with acute kidney injury and liver patterns (Trang *et al.* 1992, Muhamedhussein *et al.* 2019). Despite findings from recent studies, no definitive treatment of cerebral malaria has yet been developed beyond using antimalarial drugs and supportive care, since much of its pathogenic mechanisms remain unknown (Brejt *et al.* 2019, Luzolo *et al.* 2019, Trivedi *et al.* 2022).

### 1.2. Burden of malaria

Despite tremendous efforts to reduce malaria burden, this parasitic disease remains a significant global health problem, especially in tropical regions. It is one of the leading causes of disease and death in many developing countries. Current estimations from the World Health Organization (WHO) indicate that malaria resulted in 241 million clinical cases and 627,000 deaths in 2020 (WHO 2021). Africa carries a disproportionate burden of malaria. In 2020, with an estimated 228 million cases and 602,000 deaths, Sub-Saharan Africa accounted for about 95% of cases and 96% of deaths globally. During the same year, six highly malaria-endemic African countries including Nigeria, the Democratic Republic of the Congo, Uganda, Mozambique, Angola and Burkina Faso accounted for just over half (54%) of all malaria deaths worldwide. The global malaria case incidence remained high at 59 per 1,000 population at risk in 2020, bringing it back to the same level as 2015 after having shown a three points decrease in 2019 (WHO 2021). Health systems disruption during the COVID-19 outbreaks might have contributed to worsen the situation (Zawawi *et al.* 2020, WHO 2021, Hakizimana *et al.* 2022).

In pregnant women, malaria has an unequivocally devastating effect, including fever and severe anaemia in about 26% of women (Desai *et al.* 2007). The malaria prevalence is higher in the first and second trimester of pregnancy, accounting for a notable proportion of the total health care budget (Rogerson *et al.* 2018). Malaria is also detrimental to birth outcomes such as low birthweight (<2500g) in 8-14% of cases, preterm delivery (8-36%), and intrauterine growth retardation (13-70%). These parameters are all also associated with increased infant mortality. As a result, *P. falciparum* infection was found to be associated with some 200,000 stillbirths yearly in Sub-Saharan Africa (Moore *et al.* 2017, Saito *et al.* 2020, Chua *et al.* 2021).

Malaria occurs mostly in poor, tropical and subtropical areas of the world. The disease imposes substantial direct and indirect costs to both individual/family and governments. Direct costs including costs of illness, treatment, premature death, etc., have been estimated to be at least US $12 billion per year (CDC 2022). In these regions, it has a negative effect on economic growth and productivity: a 10% decrease in malaria incidence was associated with an increase in income per capita of about 0.3% (Sarma *et al.* 2019).

### 1.3. Malaria vectors

Malaria parasites (*Plasmodium*) are transmitted through the bite of infected female mosquitoes belonging to the genus *Anopheles*. The genus currently harbors 465 recognized species, with tremendous diversity and geographical distribution (Harbach 2007, Freitas *et al.* 2015). Of all recognized *Anopheles* species, roughly 40 have been identified as dominant malaria vectors worldwide (Hay *et al.* 2010, Sinka *et al.* 2012, WHO 2019). In Africa, members of *Anopheles gambiae* complex and the *Anopheles funestus* group are the co-dominant malaria vectors. The first comprises seven sibling species, of which *Anopheles gambiae sensu stricto* and *Anopheles arabiensis* are the most important. Because of its closeness with human, *Anopheles funestus* is the best malaria vector. In the Asian-pacific region, there is a highly complex situation with multi-species coexistence and variable species dominance (Sinka *et al.* 2012, Williams Jacob 2012).

The intensity of malaria transmission depends on factors related to the parasite, the vector, the human host and the environment. Mosquitoes' ability to transmit malaria depends firstly on the mosquito population density; secondly, on the mosquito lifespan (longevity) expressed as the likelihood that a mosquito survives through a day. Thirdly, it depends on their anthropophily, known as the preference of the female mosquito for human blood rather than of other animals; fourthly, mosquito biting rate; and lastly their susceptibility to *Plasmodium*, expressed as the mosquito competence to transmit all or some specific malaria parasites (Lefevre *et al.* 2018, WHO 2019).

Efforts to control the disease are hampered by emerging resistance of mosquitoes to the major insecticides, something that has already spread throughout Africa (Ranson *et al.* 2011, Ranson *et al.* 2016, Ondeto *et al.* 2017, Schmidt *et al.* 2018).

## 1.4. Malaria prevention

The main purpose of malaria prevention is in reducing the contact between the mosquitoes and the human host.

### 1.4.1. Vector control

Vector control is a vital component of malaria control and elimination strategies. It includes the two core vector control interventions, namely Long-lasting insecticidal nets (LLINs) and Indoor Residual Spraying (IRS); and supplementary interventions such as larval source management, topical repellents and habitat modification (WHO 2019). Evidence of the efficacy of LLINs and IRS has been demonstrated since decades in large studies (Binka *et al.* 1996, Phillips-Howard *et al.* 2003, Ter Kuile *et al.* 2003). Long-lasting insecticidal nets serve both as physical and chemical barriers protecting against mosquito bites. The WHO estimates that since the year 2000, 78% of the malaria clinical cases averted through interventions have been due to insecticidal vector control, namely through the widespread scale-up of LLINs and IRS (WHO 2019).

### 1.4.2. Preventive chemotherapies

The major target groups for preventive chemotherapies are pregnant women, young children and travelers (White *et al.* 2014, Ashley *et al.* 2018, WHO 2019). It consists of the prevention of the disease through intermittent preventive treatment in pregnancy (IPTp), intermittent preventive treatment of malaria in infants (IPTi), seasonal malaria chemoprevention (SMC), intermittent preventive treatment of malaria in school-aged children (IPTsc), post-discharge malaria chemoprevention (PDMC) and mass drug administration (MDA) (WHO 2019).

### 1.4.3. Malaria vaccine

In October 2021 the WHO recommended RTS,S/AS01, the world's first malaria vaccine, for use in children at risk in Sub-Saharan Africa and regions with moderate to high transmission of malaria caused by *P. falciparum*. Deploying this vaccine broadly is likely to contribute to saving lives (Schlagenhauf *et al.* 2008, WHO 2022).

## 1.5. Malaria treatment: severe malaria

Severe malaria is a medical emergency. With prompt and effective treatment, as well as supportive care, mortality from severe malaria, and particularly cerebral malaria falls from nearly 100% to 10-20% (WHO 2022).

The main objective of the treatment of severe malaria is to prevent the patient from dying. The prevention of disabilities and that of recrudescent infections are important secondary objectives.

Parenteral artesunate is the treatment of choice for all severe malaria including women in all trimesters of pregnancy and lactating women (Ashley *et al.* 2018, WHO 2022). Therefore, patients with severe malaria should first be treated with intravenous or intramuscular artesunate for at least 24 hours, until the patient can tolerate oral medication. Parenteral artemether and injectable quinine are alternatives where injectable artesunate is not available. Once the patient has received at least 24 hours of parenteral therapy and can tolerate oral treatment, then a full 3-days treatment course of an Artemisinin-based Combination Therapy (ACT) must be administered (WHO 2022). Parenteral artesunate has been shown to reduce mortality in both children and adults compared to parenteral quinine (Dondorp *et al.* 2005, Dondorp *et al.* 2010, Li *et al.* 2010, Sinclair *et al.* 2012, Ferrari *et al.* 2015, Ntuku *et al.* 2016). In addition, comprehensive supportive treatment, nursing and intensive care may be required (White 2022), as well as adjunctive therapy (Varo *et al.* 2018) depending on the severity of the illness.

## 1.6. Rectal artesunate

### 1.6.1. Rectal artesunate as pre-referral treatment

A full treatment course for a severe malaria episode, including initial parenteral treatment and a full course of an oral ACT, is often not accessible in remote settings or areas with a poorly functioning health care system. In addition, there will be frequently long delays in referring patients to an appropriate health facility (Gomes *et al.* 2009). In such situations, rectal artesunate (RAS) can be considered as an effective pre-referral treatment for young children. RAS rapidly (within 24 hours) clears 90% (Gomes *et al.* 2008) or more of malaria parasites. A randomized controlled trial showed that in children less than 6 years of age and who cannot reach a referral health facility in less than six hours, RAS reduced the risk of death or permanent disability by up to 50% (Gomes *et al.* 2008, Okebe *et al.* 2014). On the basis of this evidence, the WHO therefore recommended treating children less than six years of age in such circumstances with a single rectal dose of 10 mg artesunate per kilogram of body weight (WHO 2015). After the administration of RAS, the child should be referred immediately to an appropriate higher-level health facility, where the full package of care for severe malaria can be provided.

WHO and research findings in Africa consider the administration of RAS as pre-referral treatment feasible and acceptable at community level (WHO 2015, Phiri *et al.* 2016, Siribié *et al.* 2016, Warsame *et al.* 2016, Green *et al.* 2019, Mvumbi *et al.* 2019) and its administration positively affected adherence to referral advice (Mvumbi *et al.* 2019).

***History of RAS as pre-referral treatment***

The treatment with RAS is almost two decades old and has undergone an evolution over time. RAS was introduced in the WHO treatment guidelines as a pre-referral treatment for children as well as adults in 2006 (MMV 2018). In 2015, WHO issued revised guidelines by recommending that children should receive a single dose of 10 mg/kg body weight of RAS where parenteral treatment was not available and immediately be referred to an appropriate facility where the full management of severe malaria can be provided (WHO 2015).

In January 2022, a new WHO directive advised to withhold implementation of pre-referral RAS in countries that had not yet introduced pre-referral RAS and await further guidance. Likewise, it recommended stopping further expansion of its use in countries that had adopted pre-referral RAS and review in detail the conditions under which RAS was currently being used.

By the end of 2018, 48% (27 of 56) of African countries had included RAS in their national malaria treatment as pre-referral intervention for severe malaria. While 14/27 countries were in alignment with the WHO guidelines (WHO 2017); 13 countries had a different guidance for patients above 6 years, and 11 countries did not have RAS included at all (MMV 2018).

### 1.6.2. Characteristics and dosage of rectal artesunate

The WHO prequalified RAS is produced as suppositories containing 100 mg of artesunate. In accordance with the manufacturers' recommendation the dosage should be as follows: one suppository of 100 mg for children between 6 months to <3 years, and two suppositories for those from 3 to less than 6 years of age (MMV 2018). Parasite clearance kinetics is comparable between intravenous and rectal administration of artesunate (Krishna *et al.* 2001, Fanello *et al.* 2021), and better than parenteral quinine (Barnes *et al.* 2004). Compared to oral artesunate, RAS exhibits a slightly shorter time to maximal plasma concentration (Morris *et al.* 2011). This may be attributable to the fact that RAS does not have to pass through the liver, leading to a higher bioavailability after administration.

Neurotoxicity from artesunate has been observed in animals with prolonged exposure, but this was not observed in humans with a single dose (Price *et al.* 1999). Hence, RAS is considered a very safe treatment.

A rapid amelioration of children health status after RAS administration bears the risk that not all of them will successfully complete referral (Brunner *et al.* 2022), and hence sub-optimally treated at the community level. This can result in irreversible sequelae (Bangirana *et al.* 2014, Balaji *et al.* 2020), as well as a continuing disease episode with delayed treatment and suffering from long-term neurological and cognitive deficits such as epilepsy (Idro *et al.* 2010). Ultimately, this situation can also lead to the death of the patient. Hence, the question of whether RAS is beneficial to child survival needs to be investigated. This was the purpose of the CARAMAL study (Hetzel *et al.* 2022, Lengeler *et al.* 2022).

## 1.7. The Democratic Republic of the Congo: administrative and health organization

Located in central Africa, the Democratic Republic of the Congo, about the size of Western Europe, is the largest country by area in Sub-Saharan Africa (World Bank 2022). With a surface area of 2,345,409 $km^2$, it shares 9,165 km borders with nine countries: Republic of Congo (Brazzaville), the Angola's enclave of Kabinda, and a narrow 37 km Atlantic Ocean coastline to the west, Central Africa Republic and South Sudan to the north. Then Uganda, Rwanda, Burundi and Tanzania to the east, and Zambia and Angola to the south (INS 2021). With an estimated 99.2 million people, the DRC is the fourth most populous country in Africa (WPR 2022) after Nigeria, Ethiopian and Egypt.

The DRC is straddling the equator and lies between 6°North-14°South, and 12° and 32°East longitude with two third of its landmass to the south. Geographic regions include a coastal plain (West), a central basin made up of plains and stepped plateaus covered by dense forest (equatorial forest), plateaus (North, Northeast and South), where the vegetation consists of wooded savannahs interspersed with forest galleries, and mountainous massifs (East, Southeast and West) (MoH 2018).

In general, it has a warm and humid equatorial climate in the center, and a typical tropical climate in the North and South with two seasons: a "dry season" from June-August, and a rainy season from September-May. Temperatures are hot and humid in the center, cooler and drier in the southern highlands, and cooler and wetter in eastern highlands (NMCP 2014).

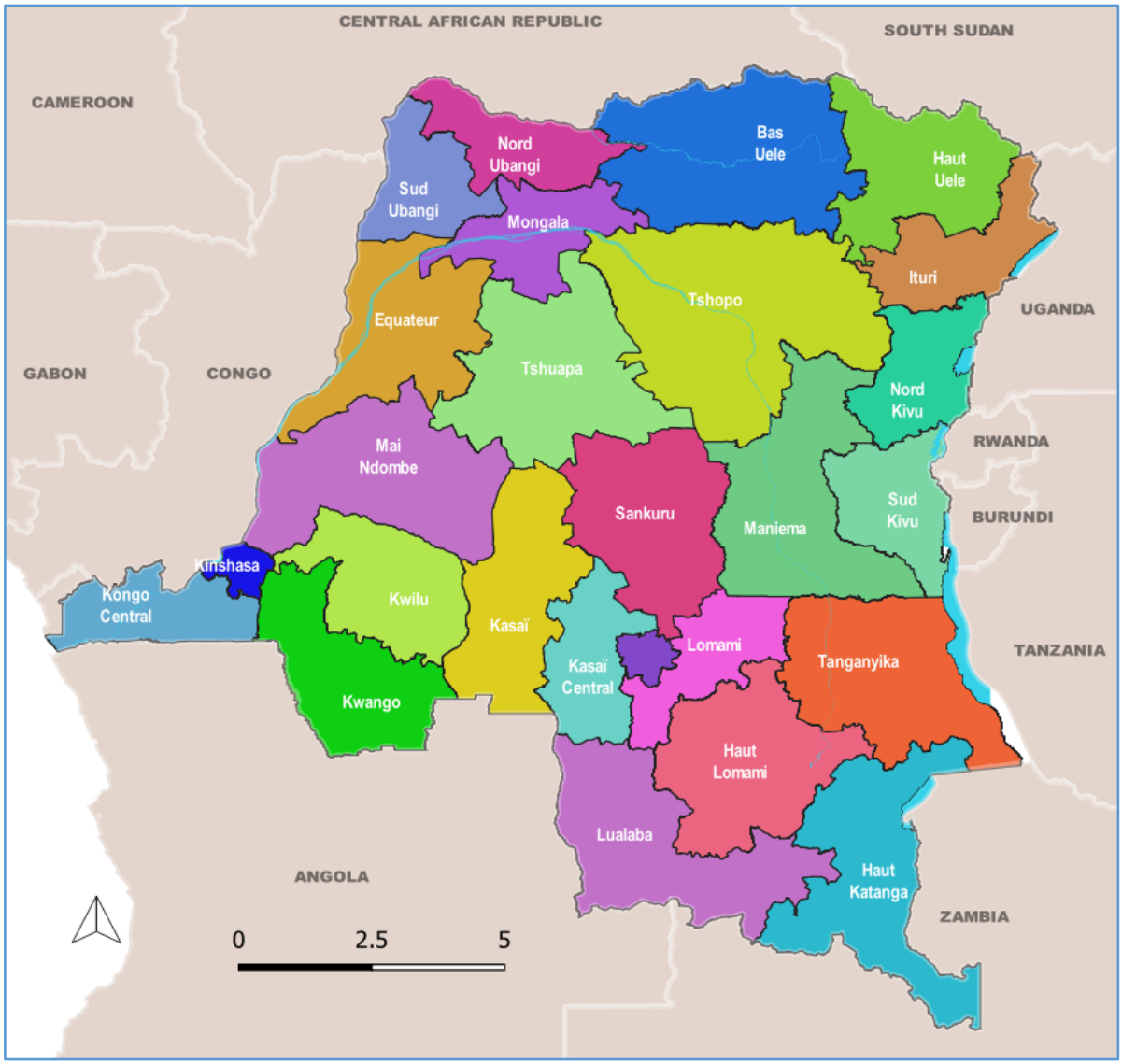
Both geographical and climatic features confer heterogeneities of malaria risk stratification across the country (high and stable in equatorial areas versus low in mountain areas).
The DRC is among the five poorest nations in the world. In 2021, with a Gross Domestic Product (GDP) per capita of US $584. Nearly 64% of the Congolese population, just under 60 million people, live on less than US $2.15 a day. About one out of six (17%) people living in extreme poverty in Sub-Saharan Africa lives in the DRC (World Bank 2021, World Bank 2022).

Under the terms of the 2006 constitution, the DRC is a highly decentralized state. It is composed of the capital city of Kinshasa and 25 provinces (Figure 1-1). This constitutional clause has been in effect since 2015. It also has 33 cities and 145 territories. Reflecting the country administrative organization, the health system is structured in three levels: central, provincial and peripheral. The first (central) is the policy making level. The provincial level provides technical support and monitoring. It comprises 26 provincial ministries of health and related provincial health divisions and health inspections. Other provincial services are provincial hospitals and laboratories, and regional drug distribution hubs.

The peripheral level comprises 516 Health Zones (HZ) that are operational units for planning and implementing the national policy. A HZ covers an average of 100,000 to 150,000 people in rural areas and 200,000 to 250,000 in urban areas. Each HZ includes a Referral Health Facility (RHF): General Reference Hospital (GRH) or a Referral Health Center (RHC), and consists of 15-20 Health Areas (HA). The last includes a Primary Health Care facility (PHC) that serves 5,000 to 10,000 people (MoH 2012). Additionally, there are Community Health Care Sites (CHCS) serving populations living in remote areas (>5km) from a health facility (HF) or isolated from the latter by a natural obstacle such as a river.

CHW work with integrated Community Case Management (iCCM) algorithms and PHC provide a minimum package of activities. By contrast, RHF offer a much more comprehensive package of care. Both public and private sectors ensure the health care provision. Public sector comprises PHC, GRH, provincial hospitals, armed forces and police hospitals, and HF owned by public companies for their employees. The private sector includes two categories: the private for-profit sector and the non-profit sector (missionary and Non-Governmental Organizations (NGO)) (MoH 2018).

***Figure 1-1**: Administrative map of the Democratic Republic of the Congo displaying 26 provinces*




## 1.8. Malaria in the Democratic Republic of the Congo

### 1.8.1. Malaria burden

Having the second highest malaria burden in the world (WHO 2021), the DRC has approximately 97% of its population living in zones with stable malaria transmission lasting 8 to 12 months per year (NMCP 2020). In 2020, the DRC accounted for 12% and 13.2% of the global malaria cases and deaths, respectively (WHO 2021). Nearly 21.3 million malaria cases were officially recorded, of whom 10.4 million were in children <5 years. Similarly, of 22,729 deaths due to malaria in 2021, 15,297 (67%) were children under the age of five (NMCP 2022).

Malaria is a major cause of admission especially for children <5 years (KSPH 2019). Progress is being made in key interventions, such as LLNI ownership and use (Ntuku *et al.* 2017). A wide variation of prevalence is observed across the country, reflecting the geographical and climatic diversity described above (Ferrari *et al.* 2016, Mwandagalirwa *et al.* 2017). With an estimated prevalence rate nationally of 20% (95% uncertainty interval [UI] 17%-23%) (Mfueni *et al.* 2018), the national-level infection rate is very high, illustrating the hyper-endemic nature of malaria in the DRC.

### 1.8.2. Malaria vector and parasite

There are two dominant vectors of malaria in the DRC including *Anopheles gambiae s.l.*, the most important species, and *An. funestus s.l.* in eastern and southeast highlands (Karch *et al.* 1992, PMI VectorLink 2020). Recently, a widespread moderate to high intensity resistance of *An. gambiae* to DDT and usual insecticides was shown (Basilua Kanza *et al.* 2013, Wat'senga *et al.* 2018, Wat'senga *et al.* 2020). To date, four *Plasmodium* species are recognized in the DRC: *P. falciparum*, the major prevalent species responsible of severe malaria (NMCP 2014, Gabrielli *et al.* 2016, Mvumbi *et al.* 2016), either as monoinfection (90.4%) or mixed with *P. malariae* (4.9%) or *P. ovale* (0.6%) (Taylor *et al.* 2011, Doctor *et al.* 2016). Recently, *P. vivax* was identified in several provinces (Kavunga-Membo *et al.* 2018, Podgorski *et al.* 2020, Brazeau *et al.* 2021, Mitchell *et al.* 2021). The prevalence of antimalarial drug resistance markers remained very low and stable (Aydemir *et al.* 2018, Deutsch-Feldman *et al.* 2019).

## 1.9. Management of malaria

Parasitological confirmation either by malaria rapid diagnostic test (mRDT) or microscopy is required prior antimalarial provision (NMCP 2018). Uncomplicated malaria should be treated with a 3-day course of an effective oral ACT. Currently, four ACTs are recommended as first-line treatment: artesunate-amodiaquine (ASAQ), artemether-lumefantrine (AL), dihydroartemisinin-piperaquine (DHA-PQ), and artesunate-pyronaridine (AP). Quinine tablet + clindamycin may be used if recommended ACT is contraindicated or not available. Injectable artesunate is the recommended treatment for severe malaria in adults, children over two months of age, and pregnant women in their second and third trimesters. Pre-referral RAS is recommended at community level, or either injectable artesunate or artemether intramuscularly if the rectal route cannot be used. The follow-on treatment for severe malaria should be made of a full course of recommended ACT for those treated with injectable artesunate or alternatively quinine tablets combined with clindamycin for those treated with quinine infusion (NMCP 2021).

# 2. Goal and objectives of the present thesis

## 2.1. Goal

To identify challenges and draw lessons learned from the implementation of pre-referral RAS in DRC, in view of supporting its responsible introduction into the national health system.

## 2.2. Objectives

1. To assess and describe comprehensively severe febrile illness/suspected severe malaria cases with regard to diagnosis, treatment and treatment outcomes, from first contact to the point of recovery or death.
2. To assess caretakers treatment seeking patterns decision-making, knowledge, and attitudes towards RAS.
3. To assess health workers compliance with severe malaria guidelines in the context of implementing pre-referral rectal artesunate.
4. To assess the costs and incremental cost-effectiveness of implementing RAS and improved case management at community level compared to the current standard of care.

# 3. Key factors predicting suspected severe malaria case management and health outcomes: an operational study in the Democratic Republic of the Congo

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## 3.1. Abstract


### Background

Evidence suggests that pre-referral Rectal Artesunate (RAS) can be a life-saving intervention for severe malaria in remote settings in Africa. Recognition of danger signs indicative of severe malaria is critical for prompt and appropriate case management.

### Methods

This was an observational study conducted in three Health Zones of the Democratic Republic of Congo to determine the distribution of dangers signs for severe malaria and assess their impact on RAS use, referral completion, injectable treatment and ACT provision, and health outcomes including death. An individual-level analysis was carried out, using multilevel-mixed effects logistic regression models. Severely ill febrile children <5 years seeking care from community-based healthcare providers were recruited into a patient surveillance system based on the presence of key danger signs. Clinical and case management data were collected comprehensively over a 28 days period. Treatment seeking was elicited and health outcomes assessed during 28 days home visits.

### Results

Overall, 66.4% of patients had iCCM general danger signs. Age of 2-5 years and iCCM general danger signs predicted RAS use (aOR = 2.77, 95% CI 2.04–3.77). RAS administration positively affected referral completion (aOR = 0.63, 95% CI 0.44–0.92).

After RAS rollout, 161 children died (case fatality ratio: 7.1%, 95% CI 6.1–8.2). RAS improved the health status of the children on Day 28 (aOR = 0.64, 95% CI 0.45-0.92) and there was a non-significant trend that mortality was higher in children not receiving RAS (aOR = 1.50, 95% CI 0.86-2.60). Full severe malaria treatment at the RHF including injectable anti-malarial and a course of ACT was highly protective against death (aOR = 0.26, 95% CI 0.09–0.79).

### Conclusions

The main findings point towards the fact that danger signs are reasonably well recognized by health provider at the primary care level, and that RAS could influence positively health outcomes of such severe disease episodes and death. Its effectiveness is hampered by the insufficient quality of care at RHF, especially the provision of a full course of ACT following

parenteral treatment. These are simple but important findings that require urgent action by the health system planners and implementers.

**Keywords:** Democratic Republic of the Congo, iCCM, IMCI, Severe malaria, Rectal artesunate, Injectable artesunate

## 3.2. Background

In 2020, an estimated 241 million cases and 627,000 deaths due to malaria occurred worldwide, of which 228 million (95%) and 602,000 (96%) were in Africa (WHO 2021). If not appropriately treated, severe malaria (SM) often leads to death or irreversible sequelae (John *et al.* 2010, Zimmerman *et al.* 2010, Bangirana *et al.* 2014, Balaji *et al.* 2020). Prompt, effective anti-malarial treatment coupled with quality supportive care can substantially reduce severe malaria mortality rates (Perry *et al.* 2014, WHO 2021), although a high average case fatality rate (CFR) of 8.7% was found in a high-quality multi-centre trial in Africa (Dondorp *et al.* 2010). One of the major challenges remains the limited access to higher-level health facilities, especially for populations living in remote areas, resulting in treatment delays of several hours or even days (Gomes *et al.* 2009, Okebe *et al.* 2014).

Injectable artesunate (AS) is the recommended first line treatment of severe malaria as compared to parenteral quinine (Dondorp *et al.* 2005, Dondorp *et al.* 2010, Sinclair *et al.* 2012, Ferrari *et al.* 2015, Ntuku *et al.* 2016). When delays in reaching referral health facilities (RHF) are expected, the World Health Organization (WHO) recommends pre-referral treatment, either with a single dose of a parenteral anti-malarial, or with a single dose of rectal artesunate (RAS)(WHO 2021). RAS is also recommended as a pre-referral treatment in the integrated community case management (iCCM) guidelines (WHO 2011, WHO 2012) and for primary health care facilities (PHC) where injectable anti-malarials are often not available (NMCP 2020, NMCP 2021, WHO 2021). In clinical settings, RAS was shown to be an excellent anti-malarial, fast acting and safe and well accepted (Angus 2020, de Carvalho *et al.* 2021, Awor *et al.* 2022). Its efficacy in reducing child mortality was shown in a large randomized placebo-controlled clinical trial in Bangladesh, Tanzania and Ghana (Gomes *et al.* 2008). However, its potential effectiveness as a life-saving intervention under real-world conditions remains to be demonstrated (von Seidlein *et al.* 2009).

The DRC has the second highest malaria mortality burden worldwide, with high average prevalence rates (NMCP 2014, Ferrari *et al.* 2016, Ferrari *et al.* 2016, Mwandagalirwa *et al.* 2017, INS 2019) almost everywhere and at least 45,000 deaths per year (WHO 2020, WHO 2021). It has a high CFR for hospitalized malaria (28%) in some settings (Mutombo *et al.* 2018), particularly in the many hard-to-reach areas of this massive country. Although the country has markedly improved both the prevention and case management of malaria in the recent decade (Lechthaler *et al.* 2019, NMCP 2020), including the implementation of iCCM packages, new interventions are urgently required to address the high number of childhood

deaths resulting from malaria. In order to achieve this, much remains to be done in better understanding the burden and patterns of severe febrile illnesses at community level, treatment seeking and its determinants, as well as the circumstance of deaths from malaria. Obviously, better management of severely ill children, who are at a high risk of dying, is of high priority to reduce the unacceptably high mortality in Congolese children. In some settings, the CFR for hospitalized severe malaria can be as high as 28% (Mutombo *et al.* 2018), which is well above the <10 % in high quality care settings (Dondorp *et al.* 2010).

The results presented here are part of the Community Access to Rectal Artesunate for Malaria (CARAMAL) project carried out in the DR Congo, Nigeria and Uganda to assess the case management for SM in remote locations and assess the public health value of RAS as a pre-referral treatment under real-world conditions (Lengeler *et al.* 2022). The design and main impact results for the three sites are presented elsewhere (Hetzel *et al.* 2022, Lengeler *et al.* 2022).

The aim of the present work was to describe for the DRC the distribution of severity signs and symptoms, among children <5 years with regard to an episode of severe febrile illness/suspected SM. In a second step, the predictive value of danger signs and symptoms on a number of main study outcomes was assessed: likelihood of RAS use, referral completion, administration of injectable artesunate in a Referral Health Facility (RHF), and health outcomes including clinical cure and mortality.

## 3.3. Methods

### Study site

This study was conducted in three rural Health Zones (HZ) in western DRC: Kenge in Kwango Province, Ipamu and Kingandu in Kwilu Province (Additional file 1: Fig. S1), with an estimated population of 786,000 inhabitants, of which 145,000 children <5 years (https://www.worldpop.org, 2018). The selection of the study areas was driven firstly by operational considerations, such as having a functioning iCCM programme supported by UNICEF, secondly by a presumably functioning referral system, and finally it had to be in an area of acceptable security. Then a sufficient population to reach the sample size calculated from an assumed baseline CFR of 6% and the ability to detect a 30% decrease in CFR following RAS roll-out was selected (Lengeler *et al.* 2022).

In the selected areas, the peripheral care system was composed of 42 functioning Community Health Care Sites (CHCS) and 152 Primary Health Care facilities (PHC) from the public, missionary and private sectors. The reference care level comprised 19 RHF including 16 Referral Health Centers and 3 General Referral Hospitals.

CHW are trained on iCCM algorithms, while nurses at PHCs follow the Integrated Management of Childhood Illness (IMCI) strategy. Both cadres provide a minimum package of preventive and curative care including RAS provision and referral of severe cases. By contrast, RHFs are staffed by medical doctors and offer a much more comprehensive package of care including blood transfusions and the management of clinical complications. Distances between CHWs and their nearest RHF were often large, with a median of distance = 17 Km (9 – 22), leading to an estimated median referral time of 2.75 hours (2.0 – 3.25). There was no organized public transportation system, so patients mainly moved by foot or bicycle.

**Study design**

CARAMAL was an observational study based on a before-and-after plausibility design (Habicht *et al.* 1999) in the framework of the RAS roll-out through established CHCS and PHC. The core of the study evaluation was a Patient Surveillance System (PSS) maintained over the two study phases: (1) pre-RAS for 10 months before RAS rollout (from June 2018 to March 2019) and (2) post-RAS that lasted 16 months after RAS introduction (from April 2019 to July 2020). The PSS allowed to enrolling eligible children since the first point of contact with the health care system and tracking them comprehensively up to Day 28. Health care providers at all levels, including CHWs, PHCs and RHFs, underwent training sessions on the effective use of RAS according to the country's iCCM and IMCI guidelines. An extensive description of the study design, sites and methods is available elsewhere (Lengeler *et al.* 2022).

**Definition of relevant danger signs**

- *iCCM general danger signs* These consisted of the general danger signs according to the iCCM algorithm and included: (1) vomiting everything, (2) convulsions, (3) not being able to drink/eat, and (4) being very sleepy or even unconscious (WHO 2012). The presence of at least one of these danger signs triggered RAS administration and immediate referral in children under 6 years old at community level (NMCP 2021, WHO 2021).

- *DRC-specific iCCM danger signs* Two additional signs/symptoms in wide use in the DRC identifying a child as being eligible for referral and hence RAS pre-referral treatment: (1) being "unable to sit or stand up" and (2) "weakness or asthenia" were also considered (Additional file 2: Fig. S2 and Table 6-2).

**Participants**

All children who were seeking care at a CHW or PHC setting that fulfilled the following inclusion criteria were enrolled: (1) children under 5 years of age, (2) fever or a history of recent fever, (3) presence of at least one of the "*iCCM general danger signs" or "DRC-specific iCCM danger signs"*, and (4) provision of signed consent by parent /guardian. Those aged more than 5 years old or without permanent resident in study area were excluded.

**Procedures**

***Enrolment***

A child fulfilling the inclusion criteria was provisionally enrolled into the PSS by a trained CHW or PHC nurse following its first contact with the health system. After a clinical assessment and a positive mRDT, the child was considered as a suspected case of SM, given RAS and referred to a designated RHF. Information such as address, child' and parent's demographics as well as clinical status of the child was reported to the study nurse based at the nearest RHF, recorded into the study database and a home visit scheduled for 28 days since provisional enrolment.

***During admission (RHF)***

The high percentage of children (67%) that successfully completed referral to a designated RHF was assessed and treated according to national guidelines (NMCP 2017). Trained CARAMAL study nurses extracted key patient information such as signs and symptoms on arrival, test results, diagnosis, treatment provided, daily clinical assessments, and condition of the child at discharge from facility records.

***Follow-up home visits***

Home visits consisted of face-to-face interview with parent/guardian and child's blood testing 28 to 30 days after provisional enrolment. Finger or heel-prick capillary blood was collected from all children for (1) malaria antigen testing (CareStartTM malaria HRP2 or HRP2/pLDH combined mRDT, Access Bio, Ethiopia), and (2) haemoglobin (Hb) level measurement

(HemoCue Hb 201, Ängelholm, Sweden). Interviews focused on the child's current health status and retrospectively recorded the history of fever, signs and symptoms, including RAS, the treatment-seeking pathway during the past 28 days and treatment(s) received. For deceased children, the circumstances and possible causes of death were elicited 4-8 weeks after their passing, to respect the mourning period.

*Data collection tools*

We used structured electronic data collection forms designed on the Open Data Kit platform (ODK, https://opendatakit.org/) to capture data at each point of contact: at day 0, during admission in a RHF, and during the day-28 home visit. Each enrolled child was assigned a unique CARAMAL identification number in order to link the data collected at different points.

**Study outcomes**

The primary outcome of this study was the child's health status on day 28 home visit as reported by his (her) parent/guardian: (healthy, still sick or deceased). Secondary outcomes consisted of three binary variable defining key elements of the case management process: (1) RAS administration (yes/no); (2) referral completion to a dedicated RHF (yes/no); (3) provision of an injectable anti-malarial treatment at the RHF (yes/no). Exposure variables of interest were the presence of the danger signs listed above, defined as a categorical variable, and including both "iCCM general danger signs" and "DRC-specific iCCM danger signs". In addition, covariates of interest included enrolment location (CHW/PHC), Health Zone (Ipamu, Kenge and Kingandu), malaria test result at the RHF (positive / negative or not done), severe anaemia (Hb < 5g/dL versus Hb ≥5g/dL), blood transfusion (yes/no), malaria oral treatment after parenteral treatment (yes/no), malaria test result on day 28 (positive / negative or not done), and anaemia (Hb < 11 g/dL versus Hb ≥11g/dL) on day 28.

**Sample size calculation and statistical analysis**

The overall sample size of the CARAMAL multi-country study was estimated for the primary outcome (mortality at Day 28) across the three project countries. The CFR was assumed to be 6% at baseline [historical CFR for severe malaria: 2.8% MATIAS Study DRC (Ferrari *et al.* 2015), 8.5% AQUAMAT (Dondorp *et al.* 2010)]. Over the three countries, a minimum of 6,032 severe malaria cases in children <5 years were required over 24 months to detect a 30% reduction in CFR between a 6 months baseline and 18 months following the roll-out of RAS,

with 80% power and $\alpha = 0.05$, as described in (Hetzel *et al.* 2022). This was a very large sample size that was amply sufficient for the analysis presented here.

Given the large sample size required for measuring the impact of RAS on CFR in each country, the sample size for the secondary analysis presented here was largely sufficient (Lengeler *et al.* 2022).

Data were analysed in STATA version 16.0 (STATA Corporation, College Station, TX, USA). An Intention-to-Treat (ITT) analysis was done, which included all participants who were formally enrolled following informed consent, and for whom day-28 follow-up data were available. The distribution of danger signs and symptoms among participants was computed, stratified in study phases (pre-RAS and post-RAS periods), as well as by RAS users and RAS non-users. Continuous variables were summarized by their mean and standard deviation (SD), or median and interquartile range (IQR) when the distribution was skewed. Dichotomous outcomes were summarized as proportions, with 95% confidence intervals (95%CI). We used the Pearson Chi square test to compare proportions. Finally, we built a multilevel-mixed effects logistic regression models for each primary and secondary outcome to adjust for potential confounders and included enrolling provider as random effect to adjust for clustering at that level. Results are presented as adjusted odd ratios (aOR) with their 95%CI.

**Ethics**

The CARAMAL study protocol was approved by the Research Ethics Review Committee of the World Health Organization (WHO ERC, No. ERC.0003008), the Ethics Committee of the University of Kinshasa School of Public Health (No. 012/2018), and the Scientific and Ethical Review Committee of CHAI (No. 112, 21 Nov 2017). The study was registered on ClinicalTrials.gov (NCT03568344). Consent was obtained provisionally from parent/guardians of the sick child prior at first point of contact. Given the urgency of the child's condition, it was not deemed adequate to perform a full informed consent at that point. This was then done once the child reached the RHF.

## 3.4. Results

### Characteristics of study participants

The study flow-chart (Additional file 3: Fig. S3) displays recruited study participants and their subsequent case management until their day-28 outcome assessment.

Key characteristics of study participants are shown in Table 3–1. Between June 2018 and July 2020, a total of 3,042 febrile children <5 years old (median age 2 years [IQR 1 - 3]) seeking care from a CHW or PHC provider were recruited into the study. Of those, 57.6% were children aged 0-2 years and 46.9% were female, with no difference in sex ratio between the pre-RAS and post-RAS periods (p=0.93).

Overall, in Kingandu HZ, significantly less children were recruited (813) compared to Kenge (1,101) and Ipamu (1,128) HZs. The vast majority of participants were enrolled at the PHC level (94.6%) rather than by CHWs (5.4%). Overall, 67% of patients successfully completed referral to a dedicated RHF, and 1/3 (33.5%) were anaemic upon arrival at the RHF, without change between the pre-RAS and post-RAS periods.

Nearly two-thirds of patients (66.4%) presented iCCM general danger signs upon enrolment (Table 3–1). This proportion rose markedly from 53.4% (pre-RAS) to 70.8% (post-RAS), p<0.001.

***Table 3-1**: Characteristics of study participants at enrolment, by study phase*

| Variable | Overall N = 3042 | Pre-RAS N = 761 | Post-RAS N = 2281 | P-value comparing pre-post RAS |
|---|---|---|---|---|
| | % | % | % | |
| **Age** | | | | 0.80 |
| 0-2 years | 57.6 | 57.2 | 57.7 | |
| 2-5 years | 42.4 | 42.8 | 42.3 | |
| **Sex** | | | | 0.93 |
| Male | 53.1 | 53.2 | 53.1 | |
| Female | 46.9 | 46.8 | 47.0 | |
| **Health Zone** | | | | <0.001 |
| Ipamu | 37.1 | 30.1 | 39.4 | |
| Kenge | 36.2 | 40.9 | 34.6 | |
| Kingandu | 26.7 | 29.0 | 26.0 | |
| **Enrolment location** | | | | <0.001 |
| CHW | 5.4 | 7.9 | 4.6 | |
| PHC | 94.6 | 92.1 | 95.4 | |
| **General iCCM danger signs** | | | | <0.001 |
| No | 33.6 | 46.7 | 29.2 | |
| Yes | 66.4 | 53.4 | 70.8 | |
| **Referral completion** | | | | 0.81 |
| No | 33.6 | 33.1 | 33.8 | |
| Yes | 66.4 | 66.9 | 66.2 | |
| **Malaria test** | | | | 0.002 |
| Negative / Not done | 47.8 | 52.7 | 46.2 | |
| Positive | 52.2 | 47.3 | 53.8 | |
| **Anaemia** | | | | 0.06 |
| No/mild anaemia/not determined | 66.5 | 69.3 | 65.6 | |
| Severe anaemia (≤5 g/dL) | 33.5 | 30.7 | 34.4 | |

CHW: Community Health Worker; PHC: Primary Health Care facility; RHF: Referral Health Facility; RAS: rectal artesunate; iCCM: integrated Community Case Management

Table 3–2 shows that "Convulsion" was the most frequent danger sign reported (40.8%), followed by "Not able to breastfeed, drink or eat anything" (36.2%) and "unusually sleepy or unconscious" (18.9%) with a significantly higher proportion of children presented during post-RAS compared to pre-RAS study phase ($p<0.001$).

Among DRC-specific iCCM danger signs, "unable to sit or stand up" was most frequently reported (26.1%), with a higher proportion during post-RAS phase ($p<0.001$).

***Table 3-2**: Danger signs triggering RAS among children <5 years recruited at community level, by study phase*

| Variable | Overall N = 3042 | Pre-RAS N = 761 | Post-RAS N = 2281 | *P-value comparing pre-post RAS* |
|---|---|---|---|---|
| | % | % | % | |
| **iCCM general danger signs** | | | | |
| Convulsions | 40.8 | 30.4 | 44.2 | <0.001 |
| Not able to breastfeed, drink or eat anything | 36.2 | 31.3 | 37.8 | 0.001 |
| Unusually sleepy or unconscious | 18.9 | 23.7 | 17.3 | <0.001 |
| Vomiting everything | 8.5 | 8.9 | 8.3 | 0.58 |
| **DRC-specific iCCM danger signs** | | | | |
| Unable to sit or stand up | 26.1 | 9.7 | 31.6 | <0.001 |
| Weakness or asthenia | 17.4 | 16.4 | 17.7 | 0.43 |

iCCM: integrated Community Case Management; RAS: rectal artesunate.

The results that follow include the use of RAS, and are therefore restricted to 2,281 patients enrolled during the post-RAS phase (April 2019 to July 2020) of the study. Tables 3, 4, 5, 6 and 7 show how key co-variates as well as the reported danger signs are associated with a number of operational and health outcomes.

**Outcome 1: RAS use**

The contribution of different predictors associated with RAS use at CHW and PHC level is shown in Table 3–3. Sick children aged 2-5 years were more likely to receive RAS compared to those aged 0-2 years (aOR = 1.58, 95% CI 1.20–2.08). There was no evidence of significant association between RAS use and gender or enrolment location. Significant heterogeneity in RAS use was observed among the three HZ. Children with one of the iCCM general danger signs were significantly more likely to receive RAS (aOR = 2.77, 95% CI 2.04–3.77), suggesting a good recognition of these signs at primary care level. The same was true for those "unable to sit" (aOR = 2.06, 95% CI 1.12–3.80), but not for children suffering from weakness or asthenia (aOR = 1.19, 95% CI 0.64–2.19).

***Table 3-3**: Determinants of RAS use by peripheral health workers*

| Determinant | N | % | Adjusted OR | 95% CI | *p*-value |
|---|---|---|---|---|---|
| **Age** | | | | | |
| 0–2 years | 1316 | 57.7 | Ref. | | |
| 2–5 years | 965 | 42.3 | 1.58 | 1.20–2.08 | 0.001 |
| **Sex** | | | | | |
| Male | 1210 | 53.0 | Ref. | | |
| Female | 1071 | 47.0 | 1.02 | 0.79–1.31 | 0.90 |
| **Enrolment location** | | | | | |
| CHW | 104 | 4.6 | Ref. | | |
| PHC | 2177 | 95.4 | 0.87 | 0.40–1.89 | 0.72 |
| **Health Zone** | | | | | |
| Ipamu | 899 | 39.4 | Ref. | | |
| Kenge | 790 | 34.6 | 0.69 | 0.41–1.18 | 0.17 |
| Kingandu | 592 | 26.0 | 0.48 | 0.28–0.84 | 0.01 |
| **Danger signs** | | | | | |
| No/Others | 415 | 18.2 | Ref. | | |
| Yes (iCCM general danger signs) | 1614 | 70.8 | 2.77 | 2.04–3.77 | <0.001 |
| Weakness or asthenia | 103 | 4.5 | 1.19 | 0.64–2.19 | 0.58 |
| Unable to sit | 149 | 6.5 | 2.06 | 1.12–3.80 | 0.02 |

N = 2,281. OR: Odds ratio; CHW: Community Health Worker; PHC: Primary Health Care facility; 95% CI: 95% confidence interval

### Outcome 2: Referral completion

Predictors associated with referral completion are presented in Table 3–4. Children in the age group of 2 to 5 years were significantly less likely to complete referral to a RHF (aOR = 0.71, 95% CI 0.54–0.93) than younger children. Compared to children enrolled by a CHW, PHC enrolments were associated with much higher odds of completing referral (aOR = 4.22, 95% CI 1.09–16.32). Since these results are controlled for signs of severity, there is clearly a differentiated recommendation between both settings. Clearly, referral completion rates appeared lower in Kenge and Kingandu compared to Ipamu HZ, but a statistically significant decrease was only observed for Kenge HZ (aOR = 0.10, 95% CI 0.03–0.29). This surprised us because Ipamu is the most remote location. Referral completion seemed only to be related to the identified "unable to sit" (aOR = 1.89, 95% CI 1.01–3.54) but not any of the other danger signs, which seem to trigger the same referral patterns. Importantly, patients who did not receive RAS were significantly less likely to complete referral (aOR = 0.63, 95% CI 0.44–0.92). Finally, using other means of transport including bicycle, motorbike and car did not show a significant association with referral completion compared to those reaching the RHF by foot.

***Table 3-4**: Estimated associations between selected determinants and referral completion*

| Determinant | N | % | Adjusted OR | 95% CI | p-value |
|---|---|---|---|---|---|
| **Age** | | | | | |
| 0–2 years | 1316 | 57.7 | Ref. | | |
| 2–5 years | 965 | 42.3 | 0.71 | 0.54–0.93 | 0.013 |
| **Enrolment location** | | | | | |
| CHW | 104 | 4.6 | Ref. | | |
| PHC | 2177 | 95.4 | 4.22 | 1.09–16.32 | 0.037 |
| **Health Zone** | | | | | |
| Ipamu | 899 | 39.4 | Ref. | | |
| Kenge | 790 | 34.6 | 0.10 | 0.03–0.29 | <0.001 |
| Kingandu | 592 | 26.0 | 0.50 | 0.17–1.50 | 0.22 |
| **Danger signs** | | | | | |
| No/Others | 415 | 18.2 | Ref. | | |
| Yes (iCCM general danger signs) | 1614 | 70.8 | 1.01 | 0.72–1.43 | 0.95 |
| Weakness or asthenia | 103 | 4.5 | 1.35 | 0.64–2.86 | 0.44 |
| Unable to sit | 149 | 6.5 | 1.89 | 1.01–3.54 | 0.08 |
| **RAS administration** | | | | | |
| Yes | 1954 | 85.7 | Ref. | | |
| No | 327 | 14.3 | 0.63 | 0.44–0.92 | 0.02 |
| **Mean of transport** | | | | | |
| Going by foot | 1910 | 83.7 | Ref. | | |
| Other mean | 371 | 16.3 | 0.89 | 0.61–1.30 | 0.56 |

N = 2,281. OR: Odds Ratio; CHW: Community Health Worker; PHC: Primary Health Care facility; 95% CI: 95% confidence interval; RAS: rectal artesunate; Ref.: Reference

### Outcome 3: Injectable treatment provision at RHF

For the injectable treatment provision outcome, we assessed determinants for the 1,511 children that completed referral successfully, and were thus eligible for injectable treatment (artesunate, artemether or quinine) while admitted (Table 3–5). There was no evidence of association between the provision of an injectable anti-malarial and age of children or enrolment location (CHW or PHC). Injectable treatment was significantly more likely to be administered in Kenge (aOR = 6.30, 95% CI 3.30–12.05). At this point of the case management process, none of the danger signs recognized at primary level seemed to be associated with injectable treatment, which was expected. On the other hand, patients treated with RAS were much more likely to receive injectable treatment (aOR = 4.75, 95% CI 3.00–7.52) and that was unexpected.

Timing of referral was not significantly associated with increased odds of injectable anti-malarial treatment provision and logically, patients tested negative for malaria or who did not have tested had much lower odds of injectable treatment provision, aOR = 0.07, 95% CI 0.04–0.11. Severe anaemia and receiving a blood transfusion were associated with a higher injectable frequency.

***Table 3-5**: Determinants of injectable antimalarial treatment for severe malaria at referral health facilities in community enrolments*

| Determinants | N | % | Adjusted OR | 95% CI | p value |
|---|---|---|---|---|---|
| **Age** | | | | | |
| Children (0–2 years) | 921 | 61.0 | Ref. | | |
| Children (2–5 years) | 590 | 39.0 | 1.13 | 0.78–1.63 | 0.53 |
| **Enrolment location** | | | | | |
| CHW | 40 | 2.7 | Ref. | | |
| PHC | 1471 | 97.4 | 0.57 | 0.17–1.91 | 0.36 |
| **Health Zone** | | | | | |
| Ipamu | 716 | 47.4 | Ref. | | |
| Kenge | 500 | 33.1 | 6.30 | 3.30–12.05 | <0.001 |
| Kingandu | 295 | 19.5 | 0.83 | 0.48–1.44 | 0.51 |
| **Danger signs** | | | | | |
| No/Others | 271 | 17.9 | Ref. | | |
| Yes (iCCM general danger signs) | 1049 | 69.4 | 1.12 | 0.70–1.78 | 0.64 |
| Weakness or asthenia | 68 | 4.5 | 1.16 | 0.45–2.98 | 0.76 |
| Unable to sit | 123 | 8.1 | 1.39 | 0.61–3.13 | 0.43 |
| **RAS administration** | | | | | |
| No | 220 | 14.6 | Ref. | | |
| Yes | 1291 | 85.4 | 4.75 | 3.00–7.52 | <0.001 |
| **Referral delay** | | | | | |
| 0 – 1 day | 1066 | 70.6 | Ref. | | |
| >1 day / Not documented | 445 | 29.4 | 1.05 | 0.71–1.55 | 0.81 |
| **Malaria test result (RHF)** | | | | | |
| Positive | 1227 | 81.2 | Ref. | | |
| Negative / Not done | 284 | 18.8 | 0.07 | 0.04–0.11 | <0.001 |
| **Anaemia at arrival at RHF** | | | | | |
| No/mild anaemia/not done | 726 | 48.1 | Ref. | | |
| Severe anaemia (≤5 g/dL) | 785 | 52.0 | 2.28 | 1.38–3.77 | 0.001 |
| **Other comorbidities** | | | | | |
| No | 802 | 53.1 | Ref. | | |
| Yes | 709 | 46.9 | 2.36 | 1.62–3.44 | <0.001 |
| **Blood transfusion** | | | | | |
| Yes | 775 | 51.29 | Ref. | | |
| No | 736 | 48.71 | 0.53 | 0.32–0.87 | 0.01 |

N = 1,511. OR: Odds ratio; CHW: Community Health Worker; PHC: Primary Health Care facility; RHF: Referral Health Facilities; RAS: rectal artesunate; 95% CI: 95% confidence intervals

**Outcome 4: Determinants of health status on day 28 (well versus still sick, among survivors)**

For this outcome, we only included children recruited during post-RAS phase of the study that still alive during home visits. Table 3–6 displays the odds to be cured versus still sick among the 2,120 children still alive on Day 28 home visits, of which 1,846 (87.1%) were healthy and 274 (12.9%) were sick. Nearly 40% of the children still had a positive mRDT on Day 28 (39.7%). It appears that age did not show evidence of association with the health status on day 28. The odds of still being sick were higher in Kenge (aOR = 1.48, 95% CI 1.05–2.07) compared to Ipamu (Ref) and lower in Kingandu (aOR = 0.62, 95% CI 0.40–0.97) compared to Ipamu. None of the initial danger signs were predictive of clinical cure on Day 28. Importantly, patients who received RAS were less likely to be sick on day 28 (aOR = 0.64, 95% CI 0.45–0.92) compared to those who did not. On the other hand, RHF treatment did not seem to make a difference to Day 28 health status in this group of children. Counter-intuitively, patients with a positive test for malaria on day 28 or with at least mild anaemia were significantly more likely to still sick at that time point (aOR = 4.67, 95% CI 3.47–6.30 and aOR = 2.01, 95% CI 1.46–2.77).

***Table 3-6**: Estimated associations between selected factors and the health status of febrile children 28 days after initial contact with the health system (cured versus still sick)*

| Determinants | N | % | Adjusted OR | 95% CI | *p*-value |
|---|---|---|---|---|---|
| **Age** | | | | | |
| Children (0–2 years) | 1198 | 56.5 | Ref. | | |
| Children (2–5 years) | 922 | 43.5 | 0.83 | 0.63–1.10 | 0.20 |
| **Health Zone** | | | | | |
| Ipamu | 842 | 39.7 | Ref. | | |
| Kenge | 734 | 34.6 | 1.48 | 1.05–2.07 | 0.02 |
| Kingandu | 544 | 25.7 | 0.62 | 0.40–0.97 | 0.04 |
| **Danger signs** | | | | | |
| No/Others | 392 | 18.5 | Ref. | | |
| Yes (iCCM general danger signs) | 1477 | 69.7 | 1.08 | 0.75–1.55 | 0.68 |
| Weakness or asthenia | 103 | 4.9 | 1.16 | 0.59–2.28 | 0.67 |
| Unable to sit | 148 | 7.0 | 1.13 | 0.61–2.12 | 0.70 |
| **RAS administration** | | | | | |
| No | 306 | 14.4 | Ref. | | |
| Yes | 1814 | 85.6 | 0.64 | 0.45–0.92 | 0.02 |
| **Injectable antimalarial** | | | | | |
| No / NA | 928 | 43.8 | Ref. | | |
| Yes | 1192 | 56.2 | 1.03 | 0.67–1.59 | 0.89 |
| **Oral antimalarial given at RHF** | | | | | |
| No | 996 | 47.0 | Ref. | | |
| Yes | 1124 | 53.0 | 1.08 | 0.68–1.72 | 0.74 |
| **Oral treatment given at discharge or prescribed** | | | | | |
| No | 1432 | 67.6 | Ref. | | |
| Yes | 688 | 32.5 | 1.12 | 0.76–1.64 | 0.58 |
| **Malaria test result on day 28** | | | | | |
| Negative / not done | 1279 | 60.3 | Ref. | | |
| Positive | 841 | 39.7 | 4.67 | 3.47–6.30 | <0.001 |
| **Anaemia (day 28)** | | | | | |
| No anaemia/not done | 790 | 37.3 | Ref. | | |
| Anaemia (Hb<11g/dL) | 1330 | 62.7 | 2.01 | 1.46–2.77 | <0.001 |

N = 2,120 alive on Day 28. OR: odds ratio; CHW: Community Health Worker; PHC: Primary Health Care facility; RHF: Referral Health Facilities; RAS: rectal artesunate; ACT: artemisinin-based combination therapy; 95% CI: 95% confidence interval; Hb: Haemoglobin; NA: not applicable (because not at RHF)

**Outcome 5: Death within 28 days after enrolment**

For the case fatality ratio calculation, all 2,281 children enrolled into the PSS during the post-RAS phase were included in the denominator. However, while assessing determinants of deaths the same sample after exclusion of 103 children that presented "weakness or asthenia", which was a danger sign that did not contribute to this outcome (death) was analysed. By the time of the Day 28 visit, a total of 161 participants were deceased among the 2,281 children in the post-RAS phase (CFR: 161/2,281 = 7.1 % (95% CI 6.1–8.2)). The great majority (137 or 85.1%) displayed iCCM general danger signs at enrolment and 24 showed other or DRC-specific iCCM danger signs (Additional file 4: Table S1). Because "weakness or asthenia" (N = 103) was shown not to be a predictor of death, these 103 children were therefore excluded, resulting in 2,178 children of whom determinants of death within 28 days following enrolment were analyzed (Table 3–7).

Compared to children between 0 to 2 years old, children of age 2 to 5 years were less likely to die (aOR = 0.44, 95% CI 0.29–0.65). The odds of dying were higher but not significantly different between children presenting iCCM general danger signs compared to those that did not show these signs (aOR = 1.57, 95% CI 0.94–2.61), while they were lower but not significantly among children "unable to sit" (aOR = 0.14, 95% CI 0.02–1.13).

The odds of dying were 1.50 times higher in patients that did receive RAS but the difference was not significant, since the confidence interval was rather large (95% CI 0.86–2.60); nevertheless, this is an encouraging finding for RAS administration. Clearly, patients with either a positive malaria test at the RHF (aOR=1.89, 95% CI 0.97–3.62) and especially with severe anaemia (aOR = 2.13, 95% CI 1.22–3.69), had increased odds of dying.

Injectable treatment given alone did not influence mortality. By contrast, the provision of an oral ACT at the RHF, given either directly or as a prescription, did offer significant protection. The full course of treatment as recommended in the national guidelines offered a high protection against dying (aOR = 0.26, 95% CI 0.09–0.79) this obviously points towards the importance of proper case management of severe malaria cases.

***Table 3-7**: Determinants of death within 28 days following enrolment*

| Determinants | N | % | Adjusted OR | 95% CI | *p* value |
|---|---|---|---|---|---|
| **Age** | | | | | |
| Children (0–2 years) | 1255 | 57.6 | Ref. | | |
| Children (2–5 years) | 923 | 42.4 | 0.44 | 0.29–0.65 | <0.001 |
| **Health Zone** | | | | | |
| Ipamu | 845 | 38.8 | Ref. | | |
| Kenge | 749 | 34.4 | 0.66 | 0.35–1.24 | 0.19 |
| Kingandu | 584 | 26.8 | 0.78 | 0.41–1.50 | 0.45 |
| **iCCM danger signs** | | | | | |
| No/Others | 415 | 19.1 | Ref. | | |
| Yes (iCCM general danger signs) | 1614 | 74.1 | 1.57 | 0.94–2.61 | 0.08 |
| Unable to sit | 149 | 6.8 | 0.14 | 0.02–1.13 | 0.07 |
| **RAS administration** | | | | | |
| No | 308 | 14.1 | Ref. | | |
| Yes | 1870 | 85.9 | 1.50 | 0.86–2.60 | 0.15 |
| **Malaria test (RHF)** | | | | | |
| Negative / Not done | 999 | 45.9 | Ref. | | |
| Positive | 1179 | 54.1 | 1.89 | 0.98–3.65 | 0.06 |
| **Anaemia on arrival at RHF** | | | | | |
| No/mild anaemia/not done | 1430 | 65.7 | Ref. | | |
| Anaemia (Hb<5 g/dL) | 748 | 34.3 | 2.13 | 1.22–3.69 | 0.008 |
| **Other comorbidities** | | | | | |
| No | 1501 | 68.9 | Ref. | | |
| Yes | 677 | 31.1 | 1.13 | 0.67–1.91 | 0.64 |
| **Injectable antimalarial** | | | | | |
| No / NA | 970 | 44.5 | Ref. | | |
| Yes | 1208 | 55.5 | 2.07 | 0.72–5.95 | 0.18 |
| **Oral antimalarial given at RHF** | | | | | |
| No | 1076 | 49.4 | Ref. | | |
| Yes | 1102 | 50.6 | 0.13 | 0.07–0.26 | <0.001 |
| **Oral treatment given at discharge or prescribed** | | | | | |
| No / NA | 1499 | 68.8 | Ref. | | |
| Yes | 679 | 31.2 | 0.53 | 0.25–1.13 | 0.10 |
| **Injectable antimalarial & ACT** | | | | | |
| No | 920 | 42.2 | Ref. | | |
| Yes | 1258 | 57.8 | 0.26 | 0.09–0.79 | 0.018 |

N = 2,178. OR: Odds ratio; CHW: Community Health Worker; iCCM: integrated Community Case Management; PHC: Primary Health Care facility; RHF: Referral Health Facility; RAS: rectal artesunate; 95% CI: 95% confidence intervals; ACT: artemisinin-based combination therapy; Hb = Haemoglobin; NA: not applicable

## 3.5. Discussion

In the CARAMAL study, the recognition of danger signs and symptoms of severe febrile illness by community-based providers (CHW and PHC) was the starting point for enrolling a child. Firstly, this allowed to assess and classify sick children according to the iCCM or IMCI algorithms (WHO 2011, WHO 2012). Secondly, it allowed initiating the proper course of action for the child, including early treatment and particularly the administration of RAS followed by a recommendation for referral to a higher-level facility. While the evaluation of the overall effectiveness of RAS is the topic of another publication (Hetzel *et al.* 2022), we here investigated the value of danger signs and other factors as predictors for appropriate case management and health outcomes, including mortality.

As with any observational study designs, this study had some methodological limitations. The analysis presented here focused on an individual patient analysis, for which many indicators were collected. To some extent, relevant confounders could be controlled for in the multivariate analysis, but it was impossible to avoid residual confounding, especially from the many health system factors that are presented below. Data on socio-economic status would certainly have been important to include in this study analysis but the decision taken was to focus on care seeking in the Day-28 interview, which could not be extended indefinitely. A second major limitation was that despite the intensity of the fieldwork it was impossible to track the clinical condition of the children continuously for 28 full days. The field staff did their best to re-construct the treatment-seeking pathway during the Day 28 interview, focusing on issues such as location of care, treatment received, and referrals, but there was certainly a risk of recall bias, despite major efforts through training and supervision. These results were then consolidated with the observations from our study nurses at the RHF, if the children were brought there. This still left some large gaps because the use of multiple providers, public and private, was the norm rather than the exception (Brunner *et al.* 2021).

In DRC, two danger signs used by health care workers were not part of the traditional iCCM general danger signs. Findings from this study suggest that the most frequently reported alternative danger sign was “unable to sit or stand up” (26.1%), which is similar to “unusually sleepy or unconscious” among the iCCM general danger signs. Of note, the relative frequency of iCCM general danger signs appeared to increase during the post-RAS phase compared to

the pre-RAS phase. This could be the results of community sensitization and training of health workers prior to RAS rollout. Unfortunately, there was no independent measure to confirm this.

Little is known from the scientific literature about the frequency and importance of danger signs and how they predict RAS provision, referral, subsequent case management at a RHF, and ultimately the child's health outcome. These are some important findings by the CARAMAL project. In an earlier multi-country cluster randomized controlled trial conducted in Ghana, Guinea-Bissau, Tanzania and Uganda using pre-referral RAS at community level (Warsame *et al.* 2016), the odds ratio of being treated with RAS when a child presented danger signs was 1.84 (95% CI 1.20-2.83); p = 0.005. These findings are consistent with our results showing that those who presented iCCM general danger signs were significantly more likely to receive RAS (aOR = 2.77, 95% CI 2.04–3.77). The trend was the same for the two additional DRC-specific signs triggering RAS use, although the association was not significant in children suffering from "weakness or asthenia". Findings from Liberia have shown that the proportions of correct diagnosis and treatment by community-based healthcare providers varied substantially for uncomplicated disease, but consistency was better for more severe cases, even though the accurate recognition of danger signs was sub-optimal (Downey *et al.* 2021). Findings from this study suggest that danger signs increase substantially the probability of receiving RAS, but not subsequent referral and treatment at a RHF. This clearly point towards the fact that the health care workers at primary level follow better the treatment guidelines than their peers in RHF.

Other reasons for the proper recognition of signs of severity and appropriate administration of RAS were observed between the three study Health Zones, due to differences in the availability of RAS (more or less stock-outs), leadership issues of local health authorities (at both HZ and PHC level), coverage in CHW and PHC within each HZ, and finally also health workers' knowledge and skills. Throughout the study implementation period, Kingandu HZ had consistently better stock of essential commodities including RAS, injectable drugs and ACT. It experienced fewer changes in leadership compared to the other two HZ, and this might be a reason for such good operational results. These results point towards the fact that complex care interventions such as the management of a severely ill child requires many health system factors to align to be successful. It also highlights the importance of doing such "real-world" intervention studies to document with some rigor these issues. However, it is unfortunately also clear than many of these operational factors cannot be fully accounted for in a quantitative

analysis because they are too many and often difficult to measure and/or quantify (such for example as the quality of leadership). Conversely, one small study in Zambia showed that when all the health system factors align properly, including transports for referrals, then CFR from malaria and other severe causes decreases massively (Green *et al.* 2019).

One of the main purposes of RAS is to allow a safer referral, since lower level health facilities and CHW are not supposed to use injectable anti-malarials. Hence, CARAMAL investigated referral determinants in detail. In contrast to result found in Uganda (Jarolimova *et al.* 2018), in DRC young patients (0-2 years), patients recruited at PHCs as well as those treated with RAS, were significantly more likely to complete referral. The fact that infants are at a higher risk of complications and especially death would almost certainly explain why younger children had higher referral rates. Similarly to the results from another study in DRC (Mvumbi *et al.* 2019), this study found that RAS administration was significantly associated with increased odds of completing referral. This contrasts with findings from a study in Uganda in which nearly all children treated with pre-referral RAS failed to comply their referral (Lal *et al.* 2018). Possibly, this may be explained in this study by the intensive sensitization of caretakers and health workers during training prior to RAS rollout. Surprisingly, no evidence was found for an association between referral completion and presence of iCCM general danger signs. This does not match evidence from another study in Uganda (Jarolimova *et al.* 2018). Additional factors based on our anecdotal experience and reported in the literature are logistics, finances of the patients, communication skills, perceived quality of care, lack of time and need to care for other children and an improvement in the child's condition (Simba *et al.* 2010, Jarolimova *et al.* 2018, Lal *et al.* 2018, Strachan *et al.* 2018). This is another example of the complexity of the decision-making process for this health-seeking step that involves a substantial time and money investment.

Findings from this study suggest that injectable treatment alone did not seem to significantly decrease the odds of dying. This is an important finding, which was also documented in the two other CARAMAL countries (Nigeria and Uganda, results not shown). RAS followed by a few doses of an injectable anti-malarial (mostly artesunate) constitutes an incomplete monotherapy treatment. Hence, it is not surprising that this makes little difference to the outcome of the child.

By contrast, oral anti-malarial treatment including an ACT or oral quinine while admitted in a RHF was very significantly associated with a large decrease in the odds of dying (by 87%). The same strong effect (a 74% reduction in the risk of dying) was seen for the combination of

parenteral malaria treatment followed by an ACT, as recommended by the WHO treatment guidelines (WHO 2021). Again, this is consistent with findings in the other two CARAMAL countries as reviewed by Signorell et al. (Signorell *et al.* 2021).

This importance of the oral anti-malarial treatment following injectable treatment in RHF is a very important finding from our study for three reasons: (1) its favorable effect on the health outcomes of these children, (2) because of the threat posed by artesunate monotherapy for the development of drug resistance (Awor *et al.* pers. commun.), and (3) because it is an actionable issue since artemisinin-based combinations are widely available in endemic countries. Finally, the odds of dying were 1.50 times higher in patients who did not received RAS, although the difference was on the margins of statistical significance. DRC key findings are consistent with findings in Nigeria and Uganda, and point towards the fact that RAS can work in reducing mortality, but it does not work well as a single intervention. RAS can only become effective in the frame of a functioning health system that includes a functioning referral system, and especially an improved quality of case management in RHFs. In contrast to previous RCTs (Gomes *et al.* 2009) demonstrating the health benefits of RAS pre-referral administration, this study demonstrates the real-world limitations of this intervention, and hence carries an important and actionable message for health authorities and the global health community.

### 3.6. Conclusions

This study aimed at describing key elements of case management for suspected severe cases of malaria, as well as the distribution of signs and symptoms among children <5 years. The differences in case management of children <5 years with different danger signs and varying treatment pathways, and related these to referral patterns, treatment at RHF, and key health outcomes including mortality were investigated. This study's main findings point towards the fact that danger signs are reasonably well-recognized by health provider at the primary care level, and that RAS could influence positively health outcomes of such severe disease episodes. Its effectiveness is clearly hampered by the insufficient quality of care at RHF, especially the provision of a full course of an ACT following parenteral treatment. These are simple but important findings, that requires urgent action by the health system planners and implementers, and which have a great potential to improve child survival in highly endemic malaria settings.

# 4. Assessing caregivers' perceptions of treatment seeking for suspected severe malaria in the Democratic Republic of the Congo

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## 4.1. Abstract


### Background

Malaria remains a major public health issue in the Democratic Republic of the Congo (DRC), accounting for 44% deaths among outpatient visits in children <5 years of age, and 22% of facility deaths. Understanding determinants of caregivers' treatment seeking patterns and decision-making is crucial in reducing the malaria burden.

### Methods

In the frame of the Community Access to Rectal Artesunate for Malaria (CARAMAL) project, cross-sectional household surveys that randomly sampled villages and households were carried-out in three rural DRC health zones prior to the rollout of pre-referral Rectal Artesunate (RAS) and then 9 and 19 months after RAS rollout (post-RAS). Data were captured electronically through face-to-face interviews with the main caregivers of children <5 years. Capillary blood samples of the children were tested for malaria and anaemia. The main study outcome was whether caregiver "sought treatment outside home" when the child had fever. Multilevel mixed effects logistic regression models using village as random effect and health zone as a fixed effect was performed to assess treatment-seeking predictors.

### Results

2,439 household interviews were completed (pre-RAS 888 and post-RAS 1,551), including 316 and 653 treatment seeking interviews. Overall, 3,499 children <5 years were tested for malaria and anaemia (pre-RAS 1,315 and post-RAS 2,184). Caregiver's recognition of severe malaria signs was poor, while knowledge of symptoms of uncomplicated malaria seemed high. Despite this, danger signs significantly increased the odds of seeking treatment (aOR=2.12, 95%CI 1.03–4.38), the same was found for the "least poor" quintile (aOR=3.01, 95%CI 1.03–8.82), as well as residents of Kingandu (aOR=2.78, 95%CI 1.01–7.65). "Doing something at home" against fever negatively affected treatment seeking in both study phases. RAS acceptance was high, at almost 100%. Malaria prevalence was higher post-RAS (45.2%) compared to pre-RAS (34.4%), p=0.003, but anaemia, although high (≥75%), was similar in both study phases (p=0.92).

**Conclusion**

In remote communities with high malaria prevalence in the DRC, malaria remain a problem. Improving the recognition of danger signs of severe disease and introducing pre-referral RAS may improve treatment seeking and contribute to reducing malaria-related mortality among children - if quality of care can be guaranteed.

**Keywords: S**evere malaria, malaria infection, rectal artesunate, treatment seeking, knowledge attitude and practice. Democratic Republic of the Congo.

## 4.2. Introduction

Several strategies are being implemented to reduce the unacceptable high burden of malaria in sub-Saharan African countries, where an estimated 228 (95%) million new malaria cases globally occurred in 2020, leading to 602'000 deaths (WHO 2021). The Democratic Republic of the Congo (DRC) accounts for 12% of that global burden of malaria (WHO 2021). Despite substantial improvements in the prevention and treatment during the past years, malaria remains the principal cause of morbidity and mortality, accounting for 44% deaths among outpatient visits in children under the age of 5, and 22% of facility deaths (NMCP 2020, U.S. President's Malaria Initiative 2022). Approximately 97% of the Congolese population lives in areas with high and stable malaria transmission, with a transmission period lasting 8 to 12 months per year (U.S. President's Malaria Initiative 2022). The most common vector encountered is *Anopheles gambiae s.l.,* and *Plasmodium falciparum* is the most common malaria parasite responsible for the majority of severe cases (NMCP 2014, U.S. President's Malaria Initiative 2022). The prevalence of malaria varies widely across the country and even within urban areas such as Kinshasa (Ferrari *et al.* 2016). A great variation was also generally observed between rural and urban areas, and across age groups (Deutsch-Feldman *et al.* 2021). The Eastern regions account for the lowest prevalence (<10%), while in zones situated in the North and the Center of the country it reaches 39% (DHS-DRC 2014, INS 2019).

To align with both international and national guidance, the National Malaria Control Program (NMCP) of DRC has developed the 2020-2023 strategic plan to guide high-impact interventions to reduce malaria-related morbidity and mortality (NMCP 2020). The interventions listed include the universal distribution of Long Lasting Insecticidal Nets (LLIN), Intermittent Preventive Treatment in pregnancy (IPTp), the treatment of severe malaria with injectable artesunate, and the treatment of uncomplicated malaria with Artemisinin-based Combination Therapies (ACT) (NMCP 2020). Despite these efforts, the malaria mortality burden remains high, particularly in children. Hence, new interventions are required, including the pre-referral treatment with RAS in children with suspected severe malaria living in remote areas. Pre-referral treatment allows to initiate antimalarial treatment soonest, and provide increased safety for the referral to a higher-level health facility (WHO 2021). Since referrals can be lengthy (Ponsar *et al.* 2011, Maketa *et al.* 2013), and any intervention to speed up the initiation of malaria treatment could potentially save lives and prevent complications.

RAS has been shown to be a safe and efficacious antimalarial medicine (Gomes *et al.* 2008, Angus 2020, de Carvalho *et al.* 2021).

A multi-country randomized controlled trial including two African countries (Ghana and Tanzania) showed that RAS was efficacious in saving lives and reducing permanent disability, when administered by community volunteers, and when the referral time to a health facility exceeded 6 hours (51% protective efficacy) (Gomes *et al.* 2009). The acceptability of RAS was universally found to be high among caregivers and community-based health workers (Phiri *et al.* 2016, Mvumbi *et al.* 2019, Angus 2020, Awor *et al.* 2022).

The Community Access to Rectal Artesunate for Malaria (CARAMAL) project was designed as a large-scale operational pilot study in three African malaria-endemic settings including the DRC, Nigeria and Uganda, to provide evidence of the real-life public health value of RAS (Lengeler *et al.* 2022). It also aimed to assess health care seeking patterns (Brunner *et al.* 2022), severe malaria case management at community and referral facility levels and describing RAS use and acceptance (Signorell *et al.* 2021, Awor *et al.* 2022, Okitawutshu *et al.* 2022). CARAMAL also assessed real world cost associated with the RAS roll-out (Lambiris *et al.* 2022). Finally, the project intended to advance the development of operational guidance to catalyze effective and appropriate scale-up of RAS as pre-referral treatment for severe malaria.

As part of the CARAMAL study, the present work aimed to (1) determine the prevalence of malaria infection and anaemia in children under 5 years of age at community level in the DRC, (2) measure the level of caregiver's knowledge and attitudes towards malaria and pre-referral rectal artesunate, and (3) understand determinants of caregiver's treatment seeking patterns and decision-making. These are essential elements in understanding the real-world effectiveness of this seemingly simple intervention used in a complex health care system, as well as optimizing its implementation at large scale in settings with limited resources.

## 4.3. Methods

### Overall study design

CARAMAL was an observational study based on a before-and-after plausibility design accompanying RAS roll-out (April 2019) in DRC, Nigeria and Uganda through established community-based health providers. The pre-RAS phase lasted 10 months prior to RAS roll-out (from June 2018 to March 2019), while the Post-RAS phase was for 16 months (from April 2019 to July 2020). A cross-sectional household survey was run 3 months prior RAS roll-out (baseline, January 2019) and then repeated 9 months (midline, January 2020) and 19 months (endline, November 2020) after RAS introduction.

### Study setting

Three cross-sectional surveys were conducted in a sample of villages within the three CARAMAL study areas in DRC: the Health Zone (HZ) of Kenge in Kwango Province, around 280 Km away from Kinshasa, as well as the Health Zones of Ipamu and Kingandu in Kwilu Province, roughly 825 Km and 650 Km from Kinshasa. The three HZs cover 933 villages (Kenge 507, Ipamu 206 and Kingandu 220) and had an estimated total population of 785'968 inhabitants, of which 145'107 were children under the age of 5 (https://www.worldpop.org). The health system included a peripheral level of care with 42 community health care sites (CHCS) and 152 primary health care facilities (PHC), as well as a reference level of care that consisted of 19 referral health facilities (RHF) - 16 referral health centers and 3 general referral hospitals. The three sites have a tropical climate with two seasons: dry season from May-September, and a rainy season from October-April. More details on the CARAMAL study settings and the study design are provided elsewhere (Lengeler *et al.* 2022), while essential impact and implementation results are also available in other publications (Signorell *et al.* 2021, Brunner *et al.* 2022, Hetzel *et al.* 2022, Okitawutshu *et al.* 2022).

### Study participants

The sampling frame consisted of all 933 villages in the three HZ in the CARAMAL project area. A multi-stage cluster sampling procedure was applied to select households. For each survey round, 32 villages (Ipamu 11, Kenge 15 and Kingandu 6; number proportional to the size of the HZ) were randomly sampled from complete village lists. In the endline survey, Ipamu HZ was not included due to logistical constraints. In each sampled village, an exhaustive

list of households with at least one child under 5 years was drawn up within the village boundaries, extended to the nearest village when the number of households was less than 30. Global positioning system (GPS) coordinates of the village boundaries were captured by data collectors in collaboration with the head of the village and CHW. Among the listed households, 30 were randomly selected to participate in the survey.

All members of sampled household were listed and a face-to-face interview about household characteristics was conducted with the household head or another adult household member. Caregivers of children under 5 years took the second section of the interview related to treatment seeking behaviour. The survey included only household heads and caregivers who had provided written informed consent. Households / caregivers without children < 5 years, those without permanent residence in the project area, and those who did not speak any of the local languages were not eligible for the interview.

**Sample size**

The sample size for the household surveys was based on a comparison of treatment seeking rates from community-based providers between baseline and post-implementation of RAS. For comparing proportions pre- and post-RAS implementation, a treatment-seeking rate at baseline was estimated conservatively to be as low as 15%, based on historic reports of treatment seeking for fever in children <5 years from formal health facilities of between 15% (Kabuya *et al.* 2014) to over 75% (Hetzel *et al.* 2008). For detecting an increase of 20% with 80% power and $\alpha = 0.05$, a minimum sample size of 906 household survey responses on treatment seeking for severe febrile illness were required per survey round.

**Rectal artesunate rollout**

World Health Organization (WHO) pre-qualified RAS suppositories each containing 100 mg of artesunate were deployed in the study areas by UNICEF, in close collaboration with national and local health authorities. Health care providers including Community Health Workers (CHWs), nurses and doctors underwent refresher trainings on the integrated community case management (iCCM) by local health authorities, with support from the National Malaria Control Programme (NMCP) and other programs implementing iCCM. These trainings focused on the recognition of iCCM general danger signs, the pre-referral treatment of suspected severe malaria with RAS at community level, and appropriate case management at referral health facilities. In parallel, a Behavior Change Communication (BCC) campaign was launched through local media with key messages on malaria, and on the benefits of seeking

health care at the nearest CHW or health facility. Following a 9 months pre-RAS phase, RAS was introduced in almost all CHWs and PHCs. The decision for RAS administration was based on iCCM guidelines (WHO 2011), and in accordance with the manufacturers' dosage recommendation: one suppository of 100 mg for children between 6 months to <3 years, and two suppositories for those from 3 to less than 6 years of age (https://www.mmv.org/research-development/project-portfolio/artecaptm). The decision criteria for a child to be given RAS included fever or a history of fever and the presence of at least one of the following iCCM general danger signs: (1) convulsions, (2) difficulty drinking or feeding, (3) repeated vomiting, and (4) unusually sleepy or unconscious (WHO 2012).

## Data collection

### Procedures

Prior to starting the survey, data collectors underwent three days of extensive training focused on the survey methodology, ethics, data collection tools and procedures. Face-to-face interviews were conducted using a pre-tested electronic structured questionnaire. All data collection tools were programmed as Open Data Kit (ODK, https://opendatakit.org/) forms on android tablet computers.

### Questionnaires

The structured household questionnaire had two sections: (1) the household information capturing demographics of all household members; age, sex, education and religion of the household head; indicators of the household's socio-economic status (household ownership of assets); LLIN coverage; household head's knowledge related to malaria. (2) Treatment-seeking patterns for an episode of fever or history of fever during the 14 days preceding the survey for those households that experienced such an episode. The treatment seeking interview captured signs and symptoms of the illness and subsequent treatment seeking patterns. It also captured data related to knowledge and attitudes of the caregivers towards RAS and their experiences with RAS.

**Blood testing**

A finger or heel-prick capillary blood sample was collected to test children <5 years for malaria, using either the CareStart$^{TM}$ Malaria Pf (HRP2) antigen test (Access Bio, Inc., Somerset, New Jersey, USA), or the SD-Bioline *P. falciparum/pf* malaria Rapid Diagnostic Test (mRDT; Standards Diagnostics, Kyonggi, Republic of Korea). In addition, haemoglobin (Hb) concentration was measured with a handheld photometer (HemoCue Hb 201+, Ängelholm, Sweden). Results were recorded in a separate ODK form.

**Study outcomes**

The primary outcome of the present study was whether caregivers "sought treatment outside home" (yes/no) when the child had fever with or without danger signs. Predictors of interest included age, sex, education, religion of child's caregiver, households' socioeconomic status (SES) expressed as wealth quintiles, presence of iCCM general danger signs, location (Heath Zone), "did something at home" (yes/no) including self-medication, cold bath, damp envelopment and any other practice to kill fever, and "took antimalarial at home" (yes/no). Secondary outcomes included the prevalence of malaria infection (mRDT positive/negative), anaemia (Hb<11 g/dL) and fever (current or history of fever in the past 48 hours preceding the survey).

**Data analysis**

Field supervisors carried out regular daily checks of the completed forms and uploaded them via internet to the secured ODK Aggregate server at the Swiss Tropical and Public Health Institute (Swiss TPH) in Switzerland. Forms were downloaded as CSV datasets from ODK Aggregate through ODK-Briefcase-v1.13.1, cleaned and analyzed in Stata SE V.16.1. (Stata Corporation, College Station, TX, USA) (StataCorp 2022). By combining household and household members' ownership of assets, livestock ownership and background characteristics of dwellings, a composite household wealth index was computed using principal components analysis (PCA) in STATA to determine households' SES in five quintiles (poorest, poor, medium, wealthy and wealthiest) (Vyas *et al.* 2006, Fry *et al.* 2014). Analysis of treatment seeking predictors was restricted to households in which the child had a history of fever in the 2 weeks preceding the survey, had already completed the treatment-seeking path, and were no longer sick.

Quantitative data was expressed as means and standard deviation (SD), or as medians and interquartile range (IQR). Means were compared using unpaired t-test or the Wilcoxon rank sum test when t-test validity criteria were not met. Categorical data was summarized as proportions with their 95% confidence intervals (95% CI), and the Pearson Chi-square test or Fisher's exact test were used to compare them. A p-value of less than 0.05 was considered statistically significant.

Crude odds ratios (OR) with their 95% CI were computed prior to building the final multilevel-mixed effects logistic regression models, using cluster (village) as random effect to adjust for clustering and including health zone as a fixed effect. Results were expressed as adjusted odd ratios (aOR) with their 95% CI. All results were divided into two study phases (pre-RAS versus Post-RAS), except for symptoms and danger signs displayed by children <5 years, which were only elicited after RAS introduction.

**Weights**

Analysis weights during the analysis were calculated as the inverse of a household / an individual's probability of being selected. The same weights were applied to household level indicators and to those related to children < 5 years within a particular household. The sampling weights were calculated by sampling stage, excluding the level of stratification that was HZ (Supplementary Table S1).

**Ethics**

The CARAMAL study protocol was approved by the Research Ethics Review Committee of the World Health Organization (WHO ERC, No. ERC.0003008), the Ethics Committee of the University of Kinshasa School of Public Health (No. 012/2018) and the Scientific and Ethical Review Committee of CHAI (No. 112, 21 Nov 2017). The study was registered on ClinicalTrials.gov (NCT03568344).

A written informed consent was obtained from all household heads prior to starting the interviews. Data collectors disclosed promptly blood test results to the child's caregiver and advised those whose children tested positive for malaria, and or those with anaemia to attend the nearest health facility for additional assessment and appropriate treatment, in accordance with national policy. Children found with severe anaemia were brought immediately to the nearest health facility by the field teams.

## 4.4. Results

### Study population

Overall, 84 villages were surveyed in the three HZ, of which 32 each at baseline and midline, and 20 at endline. The number of households sampled was 926 during the pre-RAS phase, and 1,553 during the post-RAS phase. Households with completed interviews were 888 and 1,551, respectively. In total, 969 treatment-seeking interviews were completed with caregivers of children under the age of five: 316 pre-RAS, 653 post-RAS. Of the 3,499 recorded children <5 years from whom blood samples were collected for malaria testing and Hb measurement, 1,315 were at pre-RAS and 2,184 at post-RAS (numbers shown in Supplementary Figure S1).

### Household characteristics

Table 4–1 displays household heads and household characteristics, by study phase. More than 80% of household heads were 30 years old or more. The majority of household heads were male (88.6%). Overall, 7 out of 10 household heads were of Christian faith (Catholics or other Christians), whereas one third reported being "non-Christian" including Muslims, "traditionalist", those practicing an "other religion" and very few reported having no religion at all. Concerning the highest level of education achieved, 61.3% of household heads had completed secondary school and above, while almost 10% had no education or did not answer the question. The median number of LLIN owned by household was 2 (IQR 1–3) in a subset of 1'740 households: 740 pre-RAS, 1,000 post-RAS (of which 716 from midline survey 284 from endline survey). However, this proportion appeared to decrease over-time from 3 (2–3) at pre-RAS (83.5%, 95%CI 76.4–88.8) to 2 (1–2) at post-RAS (64.6%, 95%CI 60.4–68.7), $p<0.001$. This downward trend resulted from the fact that the last LLIN distribution had taken place in 2018.

***Table 4-1**: Household heads and household characteristics, by study phase*

| Characteristics | Pre-RAS N = 888 | | Post-RAS N = 1,551 | | Pooled N = 2,439 | |
|---|---|---|---|---|---|---|
| | % | 95% CI | % | 95% CI | % | 95% CI |
| **Age** | | | | | | |
| 15-29 | 15.6 | 11.9–20.1 | 18.2 | 15.4–21.3 | 18.1 | 15.5–21.2 |
| 30-39 | 40.5 | 35.7–45.6 | 37.7 | 34.9–40.7 | 37.8 | 34.9–40.6 |
| 40-49 | 43.9 | 39.7–48.2 | 44.1 | 40.5–47.8 | 44.1 | 40.5–47.8 |
| **Sex** | | | | | | |
| Male | 87.7 | 84.9–90.1 | 88.6 | 86.0–90.8 | 88.6 | 86.0–90.7 |
| Female | 12.3 | 9.9–15.1 | 11.4 | 9.2–14.0 | 11.4 | 9.3–14.0 |
| **Religion** | | | | | | |
| Christians | 68.1 | 62.7–73.1 | 70.6 | 65.0–75.7 | 70.6 | 65.1–75.6 |
| Non-Christians | 31.9 | 26.9–37.3 | 29.4 | 24.3–35.0 | 29.4 | 24.4–34.9 |
| **Education** | | | | | | |
| No education / no answer | 12.6 | 9.1–17.4 | 10.9 | 9.1–13.0 | 10.9 | 9.1–13.0 |
| Primary | 21.3 | 16.9–26.5 | 27.9 | 24.4–31.7 | 27.8 | 24.4–31.6 |
| Secondary and above | 66.1 | 58.0–73.4 | 61.2 | 57.4–64.9 | 61.3 | 57.6–64.8 |
| **Wealth quintile** | | | | | | |
| Poorest | 26.1 | 18.2–36.0 | 21.6 | 17.8–26.0 | 21.7 | 17.9–26.0 |
| Second | 13.0 | 9.8–17.0 | 16.2 | 14.1–18.6 | 16.2 | 14.1–18.5 |
| Middle | 18.7 | 14.1–24.5 | 20.7 | 18.8–22.8 | 20.7 | 18.8–22.7 |
| Fourth | 18.4 | 15.7–21.3 | 19.8 | 17.3–22.5 | 19.8 | 17.4–22.4 |
| Least poor | 23.8 | 11.7–42.4 | 21.7 | 16.9–27.4 | 21.7 | 17.0–27.3 |
| **LLIN ownership** | **N = 740** | | **N = 1,000** | | **N = 1,740** | |
| Median (IQR) | 3 (2–3) | | 2 (1–2) | | 2 (1–3) | |

N = 2,439 households. LLIN: Long-Lasting Insecticidal Net; IQR: Interquartile range; Endline survey conducted in only two out of three health zones (see text)

**Prevalence of malaria infection and anaemia**

The proportions of children under 5 years old that had fever (axillary temperature ≥37.5 °C) or a history of fever, a malaria infection (mRDT positive) and anaemia (Hb <11 g/dL) are summarised in Table 4–2. The median age was 2–3 years and each sex represented almost half of the children surveyed. Children recruited in surveys in both study phases were similar in terms of age (rank sum test = 0.78, p = 0.44). History of fever in the last two days preceding the survey was reported in similar proportions of children at pre-RAS: 19.8% (95% CI 16.0–24.4) and post-RAS: 18.8% (95% CI 15.3–22.9), p = 0.71.

An increased temperature by axillary measurement was found in fewer cases during the pre-RAS period (4.0%, 95% CI 3.0–5.3), compared to post-RAS (6.7%, 95% CI 5.4–8.3) (p = 0.004). The prevalence of malaria infection was 34.4% (95% CI 30.1–39.0) during pre-RAS, while a significant higher positivity rate of mRDT was observed during the post-RAS phase: 45.2% (95% CI 39.8–50.7) (p =0.003). The prevalence of malaria was heterogeneous in the three health zone where surveys conducted; Kenge HZ had a significantly higher overall prevalence of malaria (66.5%) compared to Kingandu HZ (26.3%) and Ipamu HZ (7.2%), p<0.001. The observed difference above in the prevalence of malaria pre-post RAS might be in part be explained by the missing Ipamu Health Zone in the endline survey (Ipamu had generally a lower prevalence rate), and the lower coverage of LLINs (Table 1). In addition, seasonality might also reduce comparability, since the endline survey was carried out in November, corresponding to the “high transmission season”, while the baseline survey was carried out in late January and early February, during the moderate transmission period. Care should therefore be taken in interpreting the trend in the prevalence data.

A slightly higher rate of anaemia was observed pre-RAS (79.8%, 95% CI 74.0–84.5) compared to post-RAS (74.5%, 95% CI 77.0–81.7), but the difference was not statistically significant. When looking at anaemia by HZ, a similar trend than for malaria infection was observed: the highest rate was in Kenge HZ (57.5%) followed by Kingandu HZ (30.3%) and Ipamu (12.2%). The average value of haemoglobin in this young population was 9.7 (±1.6) g/dL. There was no evidence of difference in mean Hb levels between children enrolled in both study phases: pre-RAS [9.7 (±1.7) g/dL] versus post-RAS [9.7 (±1.6) g/dL]; t-test = 0.94, p = 0.35).

***Table 4-2**: Prevalence of fever, malaria infection and anaemia among children under 5 years*

| Indicator | Pre-RAS N = 1,315 | | Post-RAS N = 2,184 | | Pooled N = 3,499 | | *P-value comparing Pre-RAS and Post-RAS* |
|---|---|---|---|---|---|---|---|
| | % | 95% CI | % | 95% CI | % | 95% CI | |
| **Proportion of children <5 years with fever during the last 2 days preceding the survey** | 19.8 | 16.0–24.4 | 18.8 | 15.2–22.9 | 18.8 | 15.3–22.8 | 0.71 |
| **Proportion of children <5 years with current fever (axillary temperature ≥37.5 °C)** | 4.0 | 3.0–5.3 | 6.7 | 5.4–8.3 | 6.7 | 5.4–8.2 | 0.004 |
| **Proportion of children <5 years tested positive for malaria by mRDT** | 34.4 | 30.1–39.0 | 45.2 | 39.8–50.7 | 45.1 | 39.8–50.4 | 0.003 |
| **Proportion of children <5 years with anaemia (Hb <11 g/dL)** | 79.8 | 74.0–84.5 | 79.5 | 77.0–81.7 | 79.5 | 77.1–81.7 | 0.92 |

N = 3,499 children. 95% CI: 95% confidence interval; IQR: Interquartile range; mRDT: malaria Rapid Diagnostic Test; Hb: Haemoglobin; g/dL: gram per deciliter; Endline survey conducted in only two out of three health zones.

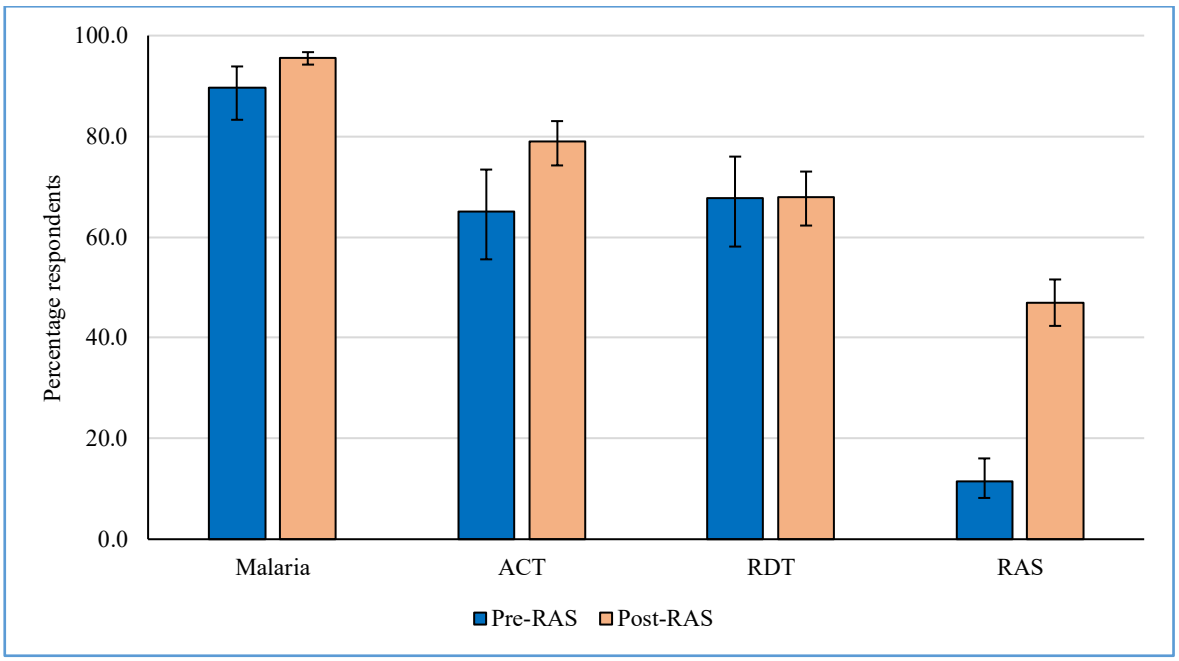
## Knowledge and attitudes towards malaria and RAS

### Knowledge of malaria, mRDT, ACT and RAS

Figure 4–1 displays the proportion of caregivers who declared having heard of malaria, mRDT, ACT and RAS, by study phase. Overall, the percentage of caregivers that reported having heard of malaria was high, and it increased significantly over time [89.7% (95%CI 83.3–93.9) at pre-RAS; 95.6% (95%CI 94.2–96.7) at post-RAS, p=0.004]. mRDT is one of the most common malaria diagnostic tools known by people seeking care at both community and health facility level in rural areas. The proportion of caregivers that reported having heard of mRDTs was almost 68% in both study phases (p=0.97). In the pre-RAS phase, 65.0% (95%CI 55.6–73.4) of caregivers mentioned they had heard of ACTs, and this proportion increased significantly

by almost 14 percent points post-RAS implementation (p=0.004). RAS was newly introduced in the study areas, and this certainly explained the lowest proportion of caregivers reporting having heard about during the pre-RAS survey (11.6%, 95%CI 8.2–16.1), while this proportion raised significantly (p<0.001) during the post-RAS surveys (47.0%, 95%CI 42.4–51.6).

***Figure 4-1**: Percentage of parents/household head declaring having heard of malaria, mRDT, ACT and RAS, by study phase*




N = 2,439 (pre-RAS, N = 888, post-RAS N = 1,551). mRDT: malaria rapid diagnostic test; ACT: artemisinin-based combination therapy; RAS: rectal artesunate

**Reported symptoms of malaria by caregiver of children <5 years**

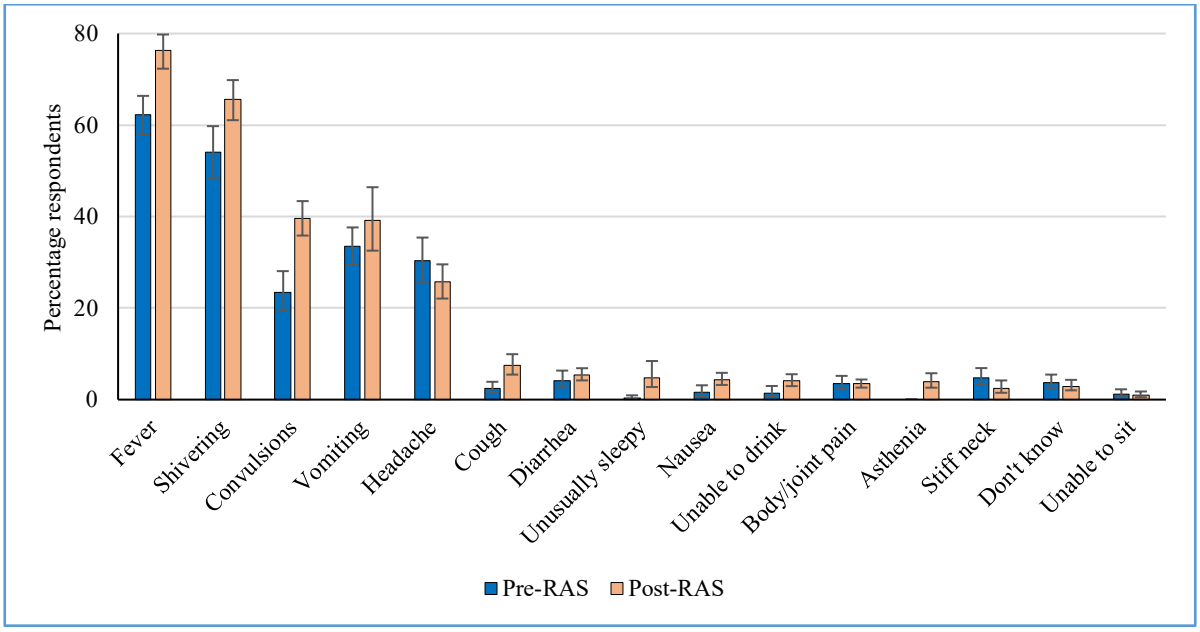
The knowledge of caregivers related to symptoms of malaria were assessed by asking them to list all symptoms of malaria they were aware of (Figure 4–2).

As might be expected, "fever" was the leading malaria symptom in all survey rounds: between 62.2% (95%CI 57.8–66.4) and 76.3% (95%CI 72.3–79.8), p<0.001. This was followed by "shivering": 54.2% (95%CI 48.4–59.8) at pre-RAS and 65.7% (95%CI 61.1–69.8) post-RAS (p=0.002). Convulsion, which is an important danger sign for severe malaria was reported by only 23.5% (95%CI 19.5–28.1) of respondents at pre-RAS and had significantly increased in the post-RAS phase (39.6%, 95%CI 35.9–43.4), p<0.001. Although community sensitization highlighted two other iCCM general danger signs including "unusually sleepy" and "unable to

drink", only few caregivers cited the first (0.3% pre-RAS versus 4.9% post-RAS), while the second ranged from 1.4% pre-RAS survey to 4.1% post-RAS.

"Vomiting" and "headache" were mentioned by one third of respondents at baseline and this increased slightly at endline for "vomiting" (39.3%), while the reverse was observed for "headache" (25.6% at post-RAS). Other common symptoms such as "diarrhoea", "nausea", "body/joint pain" and "asthenia" were reported by less than 6% of caregivers. Reported symptoms that are actually not diagnostic for malaria included respiratory symptoms such as "cough" and one sign typical for meningitis: "stiff neck".

***Figure 4-2**: Mentioned symptoms of malaria by parents/caregivers of children <5 years, by study phase*




N = 2,439 (pre-RAS, N = 888, post-RAS N = 1,551)

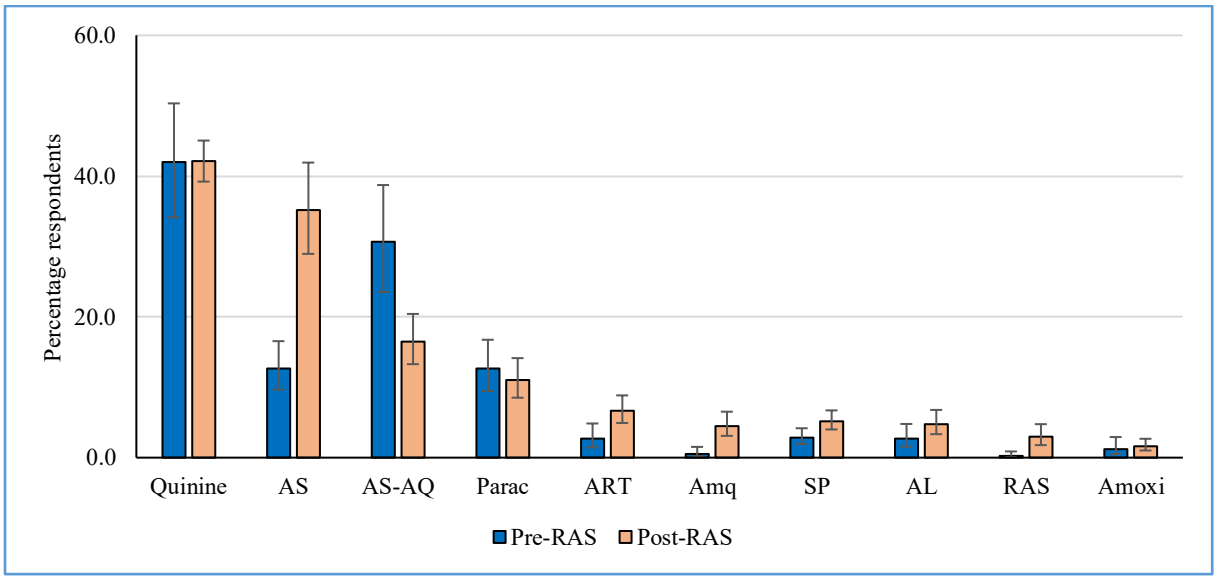
**Reported treatments for children with malaria**

Caregivers were also asked to list all treatments of malaria they were aware of (Figure 4–3). Quinine (injectable and oral) was the most frequently mentioned treatment (42.0%) in both phases of the study, followed by artesunate (12.7%, 95%CI 9.7–16.6) at pre-RAS, which significantly increased to 35.2% (95%CI 29.0–41.9) post-RAS, p<0.001. Artesunate-amodiaquine (AS-AQ) went the reverse way: 30.6% (95%CI 23.5–38.7) at pre-RAS and 16.5% (95%CI 13.3–20.4) at post-RAS, p<0.001. Sulfadoxine / pyrimethamine (SP) was reported by only 2.8% and 5.2% during the pre-RAS and post-RAS phases, respectively, p=0.010.

RAS was mentioned by only 0.2% or respondents during the pre-RAS survey, when it was basically not available; it significantly rose to 2.9% post-RAS ($p<0.001$).

This was an unexpectedly low proportion, but since RAS is only given to small children with danger signs, maybe this should have been expected. Even though amoxicillin is an antibiotic and not an antimalarial, 1.2% and 1.7% of respondents mentioned it as a malaria treatment during the pre-RAS and post-RAS phases, respectively.

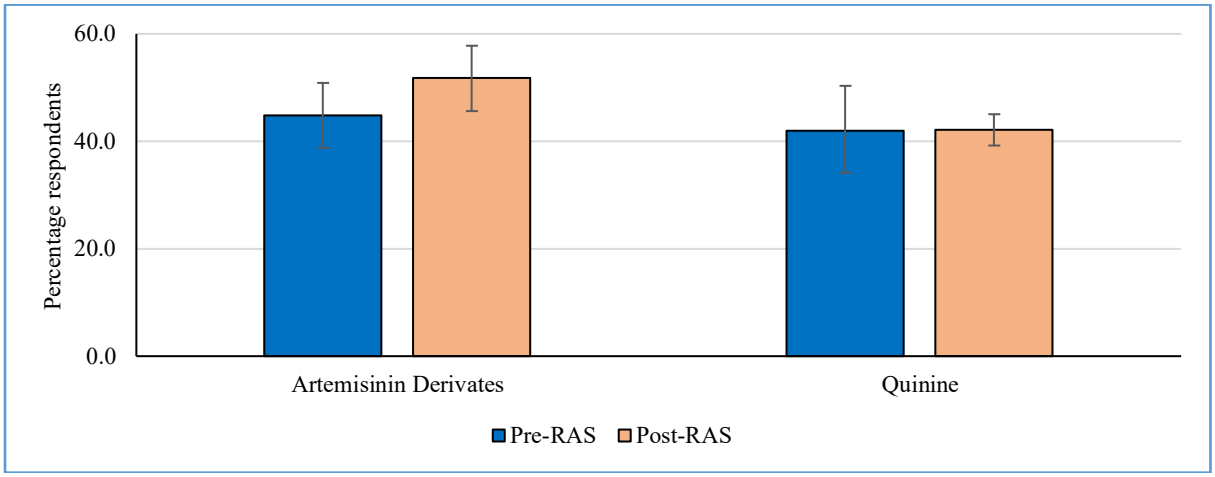
***Figure 4-3**: Mentioned treatment of child with malaria, by study phase*




N = 2,439 (pre-RAS, N = 888, post-RAS N = 1,551). AL: artemether-lumefantrine; AMq: amodiaquine; Amoxi: amoxicillin; ART: artemether; AS: artesunate; AS-AQ: artesunate-amodiaquine; Parac: paracetamol; Quinine: injectable and oral quinine; RAS: rectal artesunate; SP: sulfadoxine / pyrimethamine

Compared to quinine (injectable or oral), artemisinin derivates including injectable (artesunate, artemether) and oral (AMq, AS-AQ and AL) were more cited by caregivers (Figure 4–4).

***Figure 4-4**: Mentioned treatment of child with malaria, comparing proportions of Artemisinin derivates and quinine, by study phase*



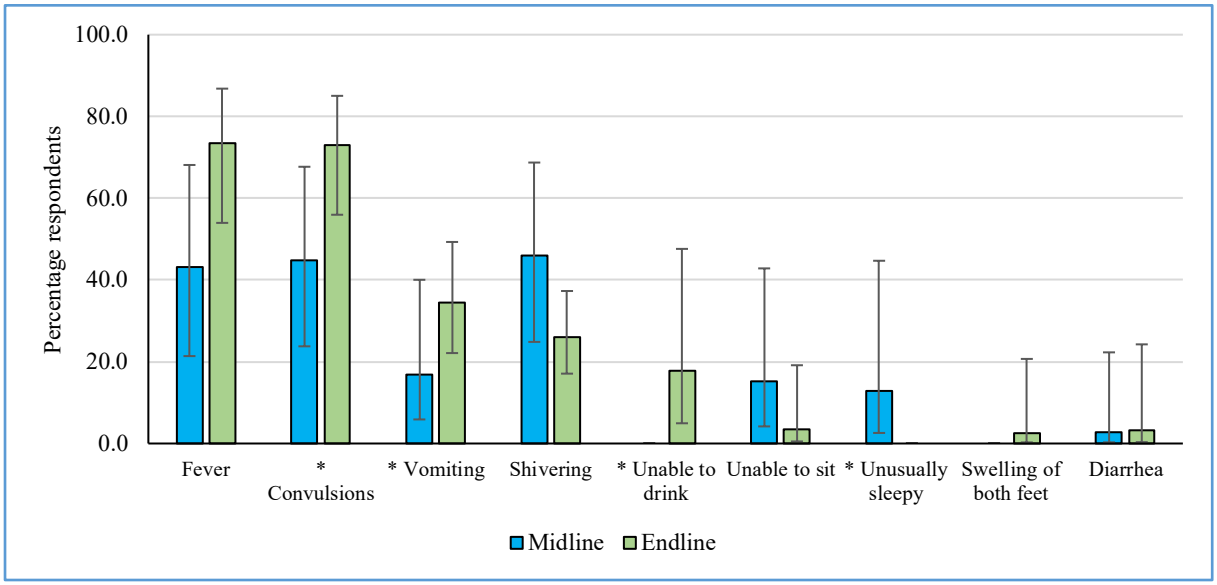

N = 2,439 (pre-RAS, N = 888, post-RAS N = 1,551). Artemisinin derivates include injectable (artesunate, artemether) and oral (amodiaquine, AS-AQ and AL). Quinine: injectable and oral quinine

**Reported symptoms and danger signs reported by caregiver when RAS was given to their child (post-RAS phase)**

During both post-RAS survey rounds, a low proportion of participants (8% at each survey, N= 665) reported that their children were given RAS by a community-based provider. Symptoms and danger signs reported for children <5 years receiving RAS are shown in Figure 4–5. Fever and convulsions were the most cited: 43.3% (95%CI 21.4–68.1) and 44.7% (95%CI 23.8–67.7) at midline, versus 73.5% (95%CI 54.0–86.8) and 72.9% (95%CI 56.0–85.0) at endline (p=0.05). "Unable to sit" was cited for 15.3% (95%CI 4.2–42.8) of the cases at midline and only 3.4% (95%CI 0.5–19.1) at endline, while swelling of both feet was only mentioned for 2.6% of cases at endline.

While reports of vomiting significantly increased between mid- and endline (17.0% versus 34.5%), the trend was inversed for shivering (46.0% versus 25.9%). "Unable to drink" was mentioned by only 17.9% (95%CI 4.9–47.6) of respondents at endline, while "unusually sleepy" was even less cited only 12.8%, (95%CI 2.6–44.7) at midline.

***Figure 4-5**: Symptoms and danger signs reported by caregiver in children <5 years when RAS was given, post-RAS phase*




N = 48 (midline N = 19, endline N = 29). *Danger sign according to iCCM guidelines

**Source of RAS per caregivers' perspective (post-RAS phase)**

When asked about the source of RAS given to their children, Primary Health Care facilities (PHCs) were reported most frequently during both survey rounds [90.6% (16/19) midline, 68.1% (17/28) endline], while provision of RAS by CHWs increased from 9.4% (3/19) at midline to 29.5% (10/28) at endline. Lastly, 93.3% (17/19) and 100.0% (28/28) of caregivers interviewed during the mid- and endline survey, respectively, declared that they would want RAS again for their child in case of illness.

**Predictors of treatment seeking outside home**

In a final analysis potential predictors related to caregivers' treatment seeking patterns and decision-making for seeking treatment outside the home for their children <5 years with fever, were assessed before and after RAS rollout. Only the subset of those whose children had a history of fever in the fourteen days prior the survey was analyzed (Table 4–3): pre-RAS 316 caregivers, merged midline and endline surveys 653 caregivers. Since caregivers were often women, this explained why the population presented in Table 4–3 was predominantly female and younger compared to the household heads shown in Table 4–1. No evidence of association with seeking treatment outside home was found for age, sex, education, religion, duration of

fever and taking antimalarials at home. Similarly, the age of the child did not show any significant association with treatment seeking, in both a univariate and a multivariate analysis. In the pre-RAS results, when compared to the poorest quintile as the reference group, the second, middle and fourth quintile of the wealth index showed some association with seeking treatment outside home, but this was not statistically significant. However, caregivers in the "least poor" quintile were more likely to search treatment outside home (aOR = 3.01, 95% CI 1.03–8.82, p = 0.045). No such evidence of association with treatment seeking was observed during the post-RAS phase, when the behavior within all quintiles seemed homogeneous and the aORs were actually below 1.

The odds of seeking treatment outside home appeared to increase - but not significantly so - at pre-RAS for Kenge and Kingandu HZ compared to Ipamu as the reference location. , At post-RAS, Kingandu residents showed an increased odds of seeking treatment outside home when their children had fever compared to those of Ipamu (aOR = 2.78, 95% CI 1.01–7.65, p = 0.047). The presence of iCCM danger signs increased significantly the odds of seeking treatment outside at pre-RAS in the un-adjusted analysis (aOR = 2.12, 95% CI 1.03–4.38, p = 0.042), but this trend was not statistically significant any more in the adjusted analysis (aOR = 1.52, 95% CI 0.89–2.61, p = 0.13).

"Doing something at home" against fever was significantly associated with a decrease in odds of seeking treatment outside home at pre-RAS (aOR = 0.24, 95% CI 0.12–0.46, p <0.001) and at post-RAS as well (aOR = 0.51, 95% CI 0.32–0.81, p = 0.005).

***Table 4-3**: Predictors of treatment seeking outside home for children <5 years with fever, before and after RAS roll-out*

| Survey round | Pre-RAS (N = 316) | | | | Post-RAS (N = 653) | | | |
|---|---|---|---|---|---|---|---|---|
| **Predictor** | **%** | **aOR** | **95% CI** | **P-value** | **%** | **aOR** | **95% CI** | **P-value** |
| **Age of caregiver (years)** | | | | | | | | |
| 15 – 29 | 41.1 | – | – | – | 31.1 | Ref. | | |
| 30 – 39 | 37.0 | – | – | – | 29.2 | 0.90 | 0.49–1.69 | 0.75 |
| ≥ 40 | 31.4 | – | – | – | 28.6 | 1.04 | 0.56–1.93 | 0.89 |
| **Sex** | | | | | | | | |
| Male | 31.5 | Ref. | | | 27.1 | Ref. | | |
| Female | 39.0 | 1.03 | 0.48–2.20 | 0.95 | 32.3 | 1.36 | 0.88–2.12 | 0.17 |
| **Education** | | | | | | | | |
| No education | 40.5 | Ref. | | | 33.4 | Ref. | | |
| Primary | 41.9 | 0.95 | 0.37–2.44 | 0.92 | 25.1 | 0.76 | 0.36–1.62 | 0.48 |
| Secondary and above | 35.7 | 0.58 | 0.26–1.30 | 0.19 | 30.4 | 0.83 | 0.41–1.70 | 0.61 |
| **Religion** | | | | | | | | |
| Christians | 35.8 | – | – | – | 27.9 | Ref. | | |
| Non-Christians | 40.8 | – | – | – | 32.6 | 1.59 | 0.96–2.64 | 0.07 |
| **Wealth quintile** | | | | | | | | |
| Poorest | 37.8 | Ref. | | | 23.2 | Ref. | | |
| Second | 49.2 | 1.92 | 0.76–4.84 | 0.17 | 27.5 | 0.54 | 0.27–1.09 | 0.09 |
| Middle | 44.5 | 1.95 | 0.77–4.92 | 0.16 | 33.4 | 0.85 | 0.44–1.65 | 0.63 |
| Fourth | 28.3 | 1.03 | 0.39–2.72 | 0.95 | 24.9 | 0.57 | 0.29–1.14 | 0.11 |
| Least poor | 33.4 | 3.01 | 1.03–8.82 | 0.045 | 35.6 | 0.68 | 0.34–1.37 | 0.28 |
| **Health Zone** | | | | | | | | |
| Ipamu | 28.1 | Ref. | | | 21.2 | Ref. | | |
| Kenge | 34.8 | 1.18 | 0.39–3.55 | 0.77 | 25.2 | 1.09 | 0.45–2.64 | 0.84 |
| Kingandu | 53.0 | 2.09 | 0.52–8.38 | 0.30 | 41.4 | 2.78 | 1.01–7.65 | 0.047 |
| **Duration of fever** | | | | | | | | |
| ≤ 2 days | 36.0 | – | – | – | 21.6 | Ref. | | |
| 3 - 4 days | 35.9 | – | – | – | 34.4 | 1.42 | 0.83–2.44 | 0.20 |
| ≥ 5 days | 41.2 | – | – | – | 28.8 | 1.29 | 0.73–2.28 | 0.39 |
| **Danger signs** | | | | | | | | |
| No | 33.9 | Ref. | | | 27.6 | Ref. | | |
| Yes | 53.7 | 2.12 | 1.03–4.38 | 0.042 | 36.9 | 1.52 | 0.89–2.61 | 0.13 |
| **Did something at home** | | | | | | | | |
| No | 66.1 | Ref. | | | 40.6 | Ref. | | |
| Yes | 26.2 | 0.24 | 0.12–0.46 | <0.001 | 25.2 | 0.51 | 0.32–0.81 | 0.005 |
| **Took antimalarials at home** | | | | | | | | |
| No | 41.7 | Ref. | | | 30.6 | Ref. | | |
| Yes | 18.2 | 0.56 | 0.23–1.37 | 0.21 | 21.0 | 0.94 | 0.47–1.91 | 0.87 |

N = 316 versus 653 caregivers (pre-RAS versus post-RAS). aOR: adjusted odds ratio; 95% CI: 95% confidence Interval

## 4.5. Discussion

The purpose of the reported study was to understand the role played by key determinants on the caregiver's treatment seeking patterns and decision-making for seeking treatment outside home for children <5 years with fever. The study also measured caregiver's level of knowledge and attitudes towards malaria and pre-referral RAS in the context of high prevalence of malaria and anaemia (DHS-DRC 2014, INS 2019).

This study had some of the limitations of observational study designs. Firstly, by restricting analysis of treatment seeking predictors to households that met certain criteria, children that were still sick were excluded, biasing potentially the assessment towards slightly less serious cases. However, since the large majority of fever cases had resolved within two weeks, this bias is likely to have been minimal. Secondly, questions on symptoms and malaria treatment did not distinguish between uncomplicated and severe malaria. Obviously, mild cases were the great majority of those reported; hence, the study's ability to describe treatment seeking for severe cases was limited. The purpose was more to get a general sense of treatment seeking and not specifically for severe cases, which was investigated in much more detail through the Patient Surveillance System set-up by CARAMAL (Hetzel *et al.* 2022). Thirdly, anaemia was defined as Hb <11 g/dL in a population relatively anaemic leading to a high prevalence of anaemia. An additional threshold of Hb <8 g/dL was added to make findings from this study more comparable with those from other DRC studies. Fourthly, the mRDT used to test for malaria detected only *Plasmodium falciparum*. Nevertheless, since this species represents over 93% of malaria cases in this region (Nundu *et al.* 2021), the missed cases would have been of marginal importance, and the symptoms of non-*falciparum* species would be anyway very similar.

Interestingly, available survey data from both study phases show that most caregivers visited the formal health facilities including PHCs and RHFs, while CHWs were not visited at all, probably due to their overall small number: only 42 across the three study HZ (Supplementary Figure S2). This was different to the other two settings of the CARAMAL study (Lengeler *et al.* 2022).

In this study, caregivers' recognition of danger signs of severe malaria is still problematic. Although their presence indicates a life threatening situation (WHO 2011), convulsions and vomiting were the only frequently cited danger signs, and these by only 40% of the caregivers in post-RAS surveys. Although they are often present in severe malaria episodes, "unusually

sleepy" and "unable to drink" were not well known despite the awareness campaigns surrounding RAS rollout. The lack of knowledge remains a challenge that need to be addressed in order to improve treatment seeking for severely ill children at community-based health providers.

Caregivers' knowledge of malaria, mRDT, ACT, and common uncomplicated malaria symptoms (fever and shivering) appeared high and was close to findings published elsewhere (Munisi *et al.* 2019, Munzhedzi *et al.* 2021, Guntur *et al.* 2022), but not in line with another study from the DRC that found lower levels of knowledge (Ntamabyaliro *et al.* 2021). Such difference can of course arise in a large country such as the DRC. Community sensitization campaigns do not seem to have resulted in malaria related knowledge increasing from pre-RAs to post-RAS, and it is therefore recommended to increase behavior change and communication campaigns (Hetzel *et al.* 2008). Different channels could be used to ensure an effective delivery of the message to a broad audience, of which nearly one third attended only primary school or had no education at all. These channels may include media, the churches whose influence on malaria control practices has been demonstrated elsewhere (Maigemu *et al.* 2015). Trained CHWs might also help spreading message during their home visits, this was already proven by other studies (Tripathi *et al.* 2016, PATH 2019). Caregivers' knowledge of malaria treatment showed that artemisinin derivatives including injectable artesunate, artemether and ACT were the most cited compared to quinine (injectable and oral). However, quinine is a well-known antimalarial, even manufactured locally in eastern DRC and often used by nearly one-third caregivers at home in early onset of malaria symptoms (Mutombo *et al.* 2014). As a result, the use of quinine is very high (see figure 4–3) considering that its use is no longer recommended by WHO and the DRC NMCP (NMCP 2017, WHO 2021). RAS was newly introduced in the study areas and hence it was not expected to be used in the pre-RAS phase. The little reported use might therefore have been due to the confusion with other suppositories or other traditional drugs or preparations commonly given to children under the age of five through the rectal route.

Only roughly, one-third of sick children were brought to care outside home within 48 hours of onset of symptoms, which is similar to other results from DRC in which where 42% of responders used a formal health facility (Ntamabyaliro *et al.* 2021). This low care seeking reflects possibly the restricted access to health facilities due to the long distances involved, and the high costs involved in malaria episodes (Kayiba *et al.* 2021). In a population in which 69.7% lives under the poverty threshold of US$ 2.15 a day (World Bank 2022), this is not surprising. As might be expected, households classified in the "least poor" quintile were more

likely to seek treatment outside home when their children had fever compared to the "poorest" quintile at baseline. This finding is consistent with those published elsewhere (Smith *et al.* 2010, Kayiba *et al.* 2021). Since SES is known to impact health care access, this was not obvious for other quintiles, which appear to be rather homogeneous due to a population structure that is also homogeneous and predominantly poor (World Bank 2022).

Although the HZ of Kingandu has a poor health facility coverage and often long distances between villages and health facilities (Okitawutshu *et al.* 2022), the stability and quality of the leadership of local health authorities could have played a key role in the significant increase of caregivers seeking treatment for their children after RAS roll-out, compared to the other two HZ.

"Doing something at home" including self-medication, cold baths, dressing and any other practices to reduce fever declined significantly the odds of seeking treatment outside home. This finding is consistent with evidence from a review of treatment seeking for malaria (McCombie 1996). With regard to the value of education, a study conducted in Zambia found a significant association between health seeking behavior and level of education (aOR = 1.47, 95% CI 1.13 – 1.92) (Apuleni *et al.* 2021), which is different to the results from this study. Another study from the DRC, however found a great proportion of participants with recommended behavior among those more educated (high school or more) (Nundu *et al.* 2021). There are no good explanations as to why this study did not observe such an association.

Given the low CHWs coverage in the study areas, RAS experience of caregivers was gathered from a limited number of them (N=48). PHC facilities were the principal source of RAS and its acceptance was high, similarly to what was found earlier in DRC (Mvumbi *et al.* 2019). Pre-RAS and post-RAS proportions of children with a history of fever (19.8% and 18.8%) was close to findings from the DRC Multiple Indicator Cluster Survey (MICS) 2018 (INS 2019) and other surveys (Nankabirwa *et al.* 2014, Ferrari *et al.* 2016), but it was lower than in the second DRC Demographic and Health Survey: 29.5% (DHS-DRC 2014).

This study found a high malaria prevalence at both study phases: pre-RAS 34.4% and post-RAS 45.2%. The prevalence of anaemia was also high, at almost 80% in both phases of the study. Hence, malaria remains a huge burden in these hard-to-reach settings, calling for high-impact interventions for both prevention and treatment.

## 4.6. Conclusion

Despite its limitations, this study highlighted the challenges related to the recognition of danger signs by caregivers of children <5 years, as well as the related treatment seeking patterns in one moderate and two high malaria prevalence settings in the DRC. Findings suggest that despite a fairly good knowledge of mild malaria symptoms and treatment, severe malaria signs (danger signs) are rather less well-known. Incorrect knowledge of symptoms of malaria are also common. This was surprising given the awareness campaigns run by the CARAMAL project. Factors such as belonging to the "least poor wealth" quintile, occurrence of danger signs (when recognized), and good leadership of health system operational unit (HZ) appeared to promote treatment seeking. In remote communities with high malaria prevalence in DRC, (severe) malaria remains a problem that needs to be addressed timely. Popularizing the recognition of danger signs of severe disease through adequate channels may enhance caregiver's decision making for treatment seeking and contribute to reducing malaria-related mortality among children – provided the quality of care can be guaranteed.

# 5. Health worker compliance with severe malaria treatment guidelines in the context of implementing pre-referral rectal artesunate in the Democratic Republic of the Congo, Nigeria and Uganda: An operational study

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## 5.1. Abstract


### Background

For a full treatment course of severe malaria, community-administered pre-referral rectal artesunate (RAS) should be completed by post-referral treatment consisting of an injectable antimalarial and oral artemisinin-based combination therapy (ACT). This study aimed to assess compliance with this treatment recommendation in children under 5 years.

### Methods and Findings

This observational study accompanied the implementation of RAS in the Democratic Republic of the Congo (DRC), Nigeria and Uganda between 2018 and 2020. Antimalarial treatment was assessed during admission in included referral health facilities (RHFs) in children under 5 with a diagnosis of severe malaria. Children were either referred from a community-based provider or directly attending the RHF.

RHF data of 7,983 children was analysed for appropriateness of antimalarials; a subsample of 3,449 children was assessed additionally for dosage and method of ACT provision (treatment compliance). A parenteral antimalarial and an ACT were administered to 2.7% (28/1,051) of admitted children in Nigeria, 44.5% (1,211/2,724) in Uganda and 50.3% (2,117/4,208) in DRC. Children receiving RAS from a community-based provider were more likely to be administered post-referral medication according to the guidelines in DRC (adjusted odds ratio (aOR) = 2.13, 95% CI 1.55-2.92, $P < 0.001$), but less likely in Uganda (aOR = 0.37, 95% CI 0.14-0.96, $P = 0.04$) adjusting for patient, provider, caregiver, and other contextual factors. While in DRC, inpatient ACT administration was common, ACTs were often prescribed at discharge in Nigeria (54.4%, 229/421) and Uganda (53.0%, 715/1,349). Study limitations include the unfeasibility to independently confirm the diagnosis of severe malaria due to the observational nature of the study.

### Conclusions

Directly observed treatment was often incomplete, bearing a high risk for partial parasite clearance and disease recrudescence. Parenteral artesunate not followed up with oral ACT constitutes an artemisinin monotherapy and may favor the selection of resistant parasites.

In connection with the finding that pre-referral RAS had no beneficial effect on child survival in the 3 study countries, concerns about an effective continuum of care for children with severe

malaria seem justified. Stricter compliance with the WHO severe malaria treatment guidelines is critical to effectively manage this disease and further reduce child mortality.

**Keywords:** Severe Malaria; Injectable Antimalarial; Artemisinin-based Combination Therapy, ACT; Compliance; Rectal Artesunate, RAS

**Summary:** Low compliance at referral health facilities to complete severe malaria treatment according to the WHO guidelines jeopardizes effective case management and beneficial effects of pre-referral rectal artesunate on favorable health outcomes including survival.

## 5.2. Introduction

Malaria deaths result from progression of uncomplicated to severe disease (Mousa *et al.* 2020).

The risk of dying is highest within the first 24 h after onset of severe symptoms (WHO 2014); therefore, prompt initiation of treatment is vital to avert severe morbidity and death. The World Health Organization (WHO) recommends treatment for severe malaria consists of an injectable antimalarial (artesunate, artemether or quinine) followed by a full course of oral artemisinin-based combination therapy (ACT) (WHO 2022).

Despite these effective and safe treatment options, many children still die from severe malaria. Two main reasons may be responsible for a fatal outcome: firstly, in several endemic countries, many children never or only belatedly reach the formal health system (Schoeps *et al.* 2011, Kadobera *et al.* 2012, Camponovo *et al.* 2017). Secondly, the quality of care that a severely ill child receives is often poor (Achan *et al.* 2011, Shah *et al.* 2016, Ampadu *et al.* 2019, Clarke-Deelder *et al.* 2019).

To increase prompt access to essential treatments, the WHO malaria treatment guidelines (WHO 2022) advise that in situations where parenteral treatment cannot be administered, a single dose of rectal artesunate (RAS) should be given, and the child be referred to a health facility where injectable treatment is available. After the WHO prequalification of two RAS products in 2018 (MMV 2018), endemic countries started to scale up RAS distribution (MMV 2018). However, evidence is scarce regarding the operational feasibility of incorporating RAS into the continuum of care for severe malaria, and the intervention's unanticipated consequences on the overall disease management. In addition, it is unclear how much impact the introduction of RAS will have under real-world circumstances (von Seidlein *et al.* 2009).

The Community Access to Rectal Artesunate for Malaria (CARAMAL) project was designed as a large-scale operational study to address these questions (Lengeler *et al.* 2022). The study aimed to assess healthcare seeking patterns (Brunner *et al.* 2022), RAS use and acceptance (Awor *et al.* 2022), anti-malarial treatment received at the various points of contact with the health system, health outcome at day 28 (Hetzel *et al.* 2022), as well as health system costs associated with the rollout of pre-referral RAS (Lambiris *et al.* 2022). Contrary to expectations, we found that RAS did not have a beneficial effect on child survival: In the DRC and Nigeria, children receiving RAS were more likely to die than those not receiving RAS (aOR=3.06, 95% CI 1.35–6.92 and aOR=2.16, 95% CI 1.11–4.21, respectively). Only in Uganda, RAS users

were less likely to be dead or sick at follow-up (aOR=0.60, 95% CI 0.45–0.79) (Hetzel *et al.* 2022). One reason for this finding may be lower referral completion in children who were administered pre-referral RAS which we found to be the case in all countries in the post-implementation phase (Brunner *et al.* 2022).

RAS on its own is insufficient to cure severe malaria. It is therefore important to understand the post-referral care and treatment patients receive in referral health facilities (RHFs).

This paper describes severe malaria treatment provided to children below 5 years in RHFs in the context of RAS rollout, and provides evidence for necessary improvements in severe malaria case management in addition to delivering this gap-filling commodity.

## 5.3. Methods

### Study design and participants

The present results were obtained in the frame of the CARAMAL project, a multi-country observational study on the implementation of quality assured pre-referral RAS by community health workers (CHWs) and primary health care facilities (PHCs). The details of the design and methods of the CARAMAL project have been published elsewhere (Lengeler *et al.* 2022). In short, CARAMAL was designed as a pre-post intervention study that started in April 2018. The post-RAS introduction period ran from April/May 2019 until August 2020. The study areas included three health zones in the DRC (Ipamu, Kenge and Kingandu), 3 Local Government Areas (LGAs) of Adamawa State in Nigeria (Fufore, Mayo-Belwa and Song), and 3 districts in Uganda (Kole, Kwania and Oyam). Local health authorities with support from UNICEF were responsible for training of healthcare providers, behaviour change and communication activities, and continuous supply of RAS.

The main data collection component of the CARAMAL study was a patient surveillance system (PSS) in which children with suspected severe malaria were provisionally enrolled upon their first contact with CHWs or PHCs.

Inclusion criteria were aligned with the criteria for administering RAS according to the country guidelines and included age under 5 years, history of fever, plus at least one danger sign defining a severe febrile illness episode according to the national iCCM guidelines (not able to drink or feed anything, unusually sleepy or unconscious, convulsions, vomits everything).

Following provisional enrolment of an eligible patient, basic information on inclusion criteria, RAS administration and referral was transmitted to the study team by the healthcare worker according to country-specific notification routes, and captured in electronic study forms and registers. Patients who were successfully referred from a CHW or PHC to the RHFs in the study areas were identified and monitored by trained study nurses based at each of the study areas' 25 RHFs. For a comprehensive assessment of severe malaria treatment at included RHFs, we also enrolled children below the age of 5 directly attending such RHFs and diagnosed with severe malaria. Only patients diagnosed with severe malaria by RHF clinicians were included in this analysis; the diagnosis was, however, not verified for correctness. Children receiving outpatient antimalarial treatment at RHFs (mainly Uganda) were not included in this study.

All monitored RHFs were public or private not-for-profit institutions, including health centre level IV and hospitals in Uganda, cottage hospitals in Nigeria and referral health centre and general reference hospitals in DRC.

A follow-up visit at patients' homes was scheduled 28 days after enrolment for all children enrolled into the study, which included a structured interview about the patient's health status, signs and symptoms of the disease, and treatment-seeking.

**Study procedures**

Case management information was extracted from patients' hospital records by trained study staff and complemented by direct observation and information obtained from resident hospital staff. Inpatient treatment data was transcribed in real-time on paper forms and then copied onto tablets using structured electronic forms in ODK Collect (https://opendatakit.org/). An updated data collection form implemented two (Nigeria) to four (DRC, Uganda) months after the roll-out of RAS also included drug type, route and dates and times of antimalarial therapy and details of ACT prescription / dispensing at discharge. Health status, as well as the payment scheme for hospitalization and medication (artesunate and ACT were supposed to be free of charge) were recorded upon hospital release. Information on the use of pre-referral RAS was consolidated from different data sources (enrolment register, RHF and day 28 data collection forms) through the different points of contact with the healthcare system (CHW, PHC, RHF) and from a caregiver's interview on day 28.

**Definitions**

The definitions used for measurement of compliance outcomes are shown in Figure 5–1. Medication appropriateness was defined as administration of recommended parenteral antimalarials, including artemisinin, artemether or quinine, plus oral ACTs (at least one dose of each); medication appropriateness was computed for the entire study population. Treatment compliance was defined as provision of at least 3 doses of an appropriate parenteral antimalarial (artesunate, artemether or quinine) followed by administration, dispensing or prescription of an ACT; treatment compliance was assessed for data from a post-implementation sub-sample for which the updated, more comprehensive data collection form was used.

**Statistical analysis**

Analyses were planned in January 2021, after completion of data collection. Results were stratified by country and enrolment location and calculated as overall proportions. Proportions were compared by $\chi^2$ test.

Age, sex, weight, pre-referral RAS administration, treatment seeking and malaria test result were considered as potential patient-level predictors of medication appropriateness. Caregivers were asked a yes/ no question about whether they had to pay any fees either for hospitalization or for medication; this was analysed as provider-level predictor; contextual predictors comprised study country, study area and seasonality. Upon peer review of the manuscript, caregiver age was added as an important predictor; since the variable "highest level of education completed" had 51% missing data it was not included in the model. Potential predictors for medication appropriateness were determined by a logistic regression model with a binary outcome variable equal to 1 for appropriate medication. We report a multivariable model adjusting for all other predictors. All models were based on complete cases. In addition, we also did a sensitivity analysis using multiple imputation methods for weight, which had 12.4% missing values of the total sample. There were no differences in the results and we therefore only report results based on the complete cases.

All analyses were performed using Stata/MP 16.1 (StataCorp, College Station, Texas, USA). This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (S1 STROBE Checklist).

## Ethics statement

The CARAMAL study protocol was approved by the Research Ethics Review Committee of the World Health Organization (WHO ERC, No. ERC.0003008), the Ethics Committee of the University of Kinshasa School of Public Health (No. 012/2018), the Health Research Ethics Committee of the Adamawa State Ministry of Health (S/MoH/1131/I), the National Health Research Ethics Committee of Nigeria (NHREC/01/01/2007-05/05/2018), the Higher Degrees, Research and Ethics Committee of the Makerere University School of Public Health (No. 548), the Uganda National Council for Science and Technology (UNCST, No. SS 4534), and the Scientific and Ethical Review Committee of CHAI (No. 112, 21 Nov 2017). The study is registered on ClinicalTrials.gov (NCT03568344). Only patients whose caregivers provided written informed consent were enrolled in the study.

## Inclusivity in global research

Additional information regarding the ethical, cultural, and scientific considerations specific to inclusivity in global research is included in the Supporting Information (S2 PLOS policy and questionnaire).

## 5.4. Results

### Characteristics of patients

Between April 2018 and July 2020, 14,911 children were provisionally enrolled into the PSS. For 6,928 children caregivers either did not provide consent, children were not admitted to one of the RHFs monitored by the study team, or did not have a diagnosis of severe malaria at admission. Hence, 7,983 children were included in this analysis (Figure 5–1). For 3,449 (43.2%) of them, more detailed case management data was recorded with an updated data collection form.

**Figure 5–1. Details of analysis dataset and definitions of antimalarial treatment compliance.** Of the 14,911 children enrolled in the CARAMAL study (either by a community-based provider or at the RHF), 7,983 underwent treatment at a RHF and were included in the analysis (2,257 enrolled during the RAS pre-implementation period (pre-RAS), 5,726 enrolled after RAS was rolled out (post-RAS)). 1,600 received pre-referral RAS during the post-RAS phase, 4,126 did not. Medication appropriateness was assessed for the full dataset (highlighted in light grey), treatment compliance was analysed for the post-implementation subsample (shown with blue background).

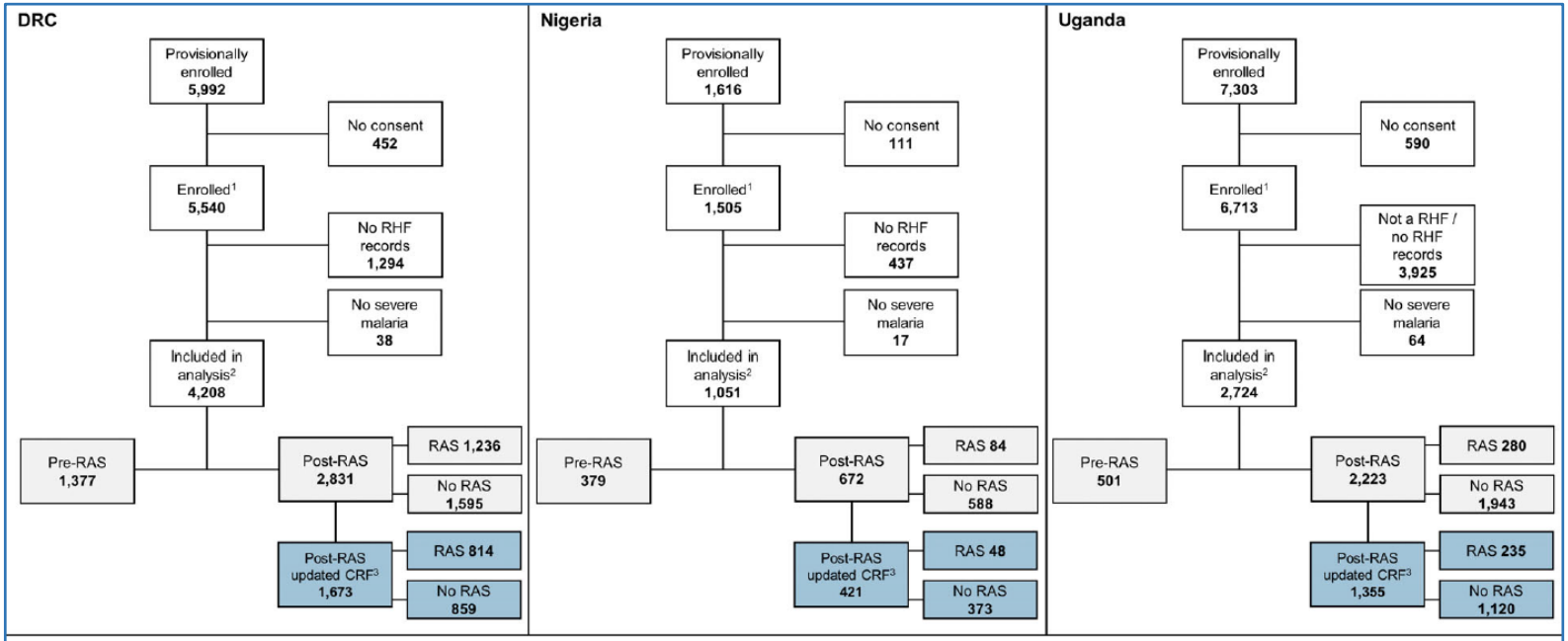
ACT, artemisinin-based combination therapy; CRF, case report form; DRC, Democratic Republic of the Congo; RHF, referral health facility; RAS, rectal artesunate

[1] Enrolled in CARAMAL study by community-based provider or directly enrolled at RHF

[2] Followed up after admission to RHF

[3] Post-RAS subsample with more detailed treatment data

***Figure 5-1**: Details of analysis dataset and definitions of antimalarial treatment compliance*




| Definition | | Study period |
|---|---|---|
| Treatment compliance | Medication appropriateness: At least one dose of an injectable antimalarial (artesunate, artemether or quinine) and at least one dose of an ACT (artemether-lumefantrine, artesunate-amodiaquine) while the patient was still hospitalised | Full |
| | Treatment compliance: At least three doses of an injectable antimalarial (artesunate, artemether or quinine), followed by at least one dose of an ACT (artemether-lumefantrine, artesunate-amodiaquine) administered by health workers during admission, or administered by health workers during admission or prescribed / dispensed at RHF discharge | Post-implementation (updated data collection tool) |

Table 5–1 (full sample) and Supplementary Table 5–1 (sub-sample) show baseline characteristics of the children included in this analysis. 2,381 (29.8%) children undergoing treatment at a RHF were enrolled by a community-based healthcare provider (CHW, PHC) while 5,602 (70.2%) were enrolled directly at a RHF. Among the children enrolled by a community-based provider during the post-RAS implementation period, the proportion who received a dose of pre-referral RAS was higher in DRC (82.6%, 1,188/1,939) and Uganda (73.2%, 123/225) than in Nigeria (44.2%, 80/217).

**Parenteral treatment**

Across the full study period, most of the children were treated with an injectable antimalarial at RHFs (DRC 83.7% (3,521/4,208), Nigeria 93.6% (984/1,051) and Uganda 94.8% (2,583/2,724); Table 5–2). In 86.8% of these cases (6,153/7,088), injectable artesunate was administered. During the post-implementation period, administration of parenteral antimalarials was higher than in the pre-implementation period (Figure 5–2, Table 5–2). In DRC, the use of intravenous quinine was still common (18.3% among all children (N=4,208) though it was gradually replaced by artesunate throughout study duration (34.6% (476/1,377) pre-implementation, 10.3% (292/2,831) post-implementation). Strikingly, during both study periods the use of quinine was relatively more common in children directly attending a RHF compared to community referrals (56.2% (360/641) vs. 37.3% (116/311) pre-implementation, 14.1% (179/1,267) vs. 8.7% (113/1,302) post-implementation, both $P < 0.001$).

***Table 5-1**: Summary characteristics of surveyed patients and exposure variables*

| | DRC | | Nigeria | | Uganda | |
|---|---|---|---|---|---|---|
| | **Community enrolments N = 1,939** n (%) | **RHF enrolments N = 2,269** n (%) | **Community enrolments N = 217** n (%) | **RHF enrolments N= 834** n (%) | **Community enrolments N = 225** n (%) | **RHF enrolments N = 2,449** n (%) |
| **Age (years)** | | | | | | |
| < 1 | 428 (22.1) | 475 (20.9) | 19 (8.8) | 91 (10.9) | 46 (20.4) | 495 (19.8) |
| 1 - 2 | 996 (51.4) | 1115 (49.1) | 134 (61.8) | 474 (56.8) | 136 (60.4) | 1377 (55.1) |
| 3 - < 5 | 515 (26.6) | 679 (29.9) | 64 (29.5) | 269 (32.3) | 43 (19.1) | 627 (25.1) |
| **Sex** | | | | | | |
| Female | 931 (48.0) | 1053 (46.4) | 76 (35.0) | 367 (44.0) | 106 (47.1) | 1122 (44.9) |
| **RAS implementation period & pre-referral RAS use** | | | | | | |
| Pre-implementation | 501 (25.8) | 876 (38.6) | 36 (16.6) | 343 (41.1) | 57 (25.3) | 444 (17.8) |
| RAS use: yes | 3 (0.6) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 2 (3.5) | 6 (1.4) |
| RAS use: no | 498 (99.4) | 874 (99.8) | 36 (100.0) | 343 (100.0) | 55 (96.5) | 438 (98.7) |
| Post-implementation | 1438 (74.2) | 1393 (61.4) | 181 (83.4) | 491 (58.9) | 168 (74.7) | 2055 (82.2) |
| RAS use: yes | 1188 (82.6) | 48 (3.5) | 80 (44.2) | 4 (0.8) | 123 (73.2) | 157 (7.6) |
| RAS use: no | 250 (17.4) | 1345 (96.6) | 101 (55.8) | 487 (99.2) | 45 (26.8) | 1898 (92.4) |
| **Malaria test*** | | | | | | |
| positive (mRDT or blood slide) | 1695 (87.4) | 2007 (88.5) | 197 (90.8) | 740 (88.7) | 222 (98.7) | 2477 (99.1) |
| negative / not done | 244 (12.6) | 262 (11.6) | 20 (9.2) | 94 (11.3) | 3 (1.3) | 22 (0.9) |
| **Rainy season°** | 1096 (56.5) | 1113 (49.1) | 159 (73.3) | 547 (65.6) | 156 (69.3) | 1723 (69.0) |
| **Drugs payable** | 863 (46.5) | 1005 (54.3) | 144 (72.0) | 543 (78.1) | 35 (15.6) | 419 (16.8) |
| missing | 84 (4.3) | 418 (18.4) | 17 (7.8) | 139 (16.7) | 0 (0.0) | 0 (0.0) |
| **Hospitalization payable** | 874 (47.1) | 859 (46.4) | 33 (16.5) | 76 (10.9) | 10 (4.4) | 394 (15.8) |
| missing | 84 (4.3) | 418 (18.4) | 17 (7.8) | 139 (16.7) | 0 (0.0) | 0 (0.0) |
| **Age caregiver (years)** | | | | | | |
| < 30 | 576 (29.7) | 806 (35.6) | 108 (49.8) | 378 (45.3) | 148 (65.8) | 1529 (61.2) |
| ≥ 30 | 1363 (70.3) | 1461 (64.5) | 109 (50.2) | 456 (54.7) | 77 (34.2) | 969 (38.8) |
| missing | 0 (0.0) | 2 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| **Education caregiver** | | | | | | |
| Completed secondary education | 563 (59.8) | 560 (63.4) | 36 (33.6) | 95 (29.6) | 12 (8.5) | 177 (11.8) |
| Completed primary education | 183 (19.5) | 186 (21.0) | 18 (16.8) | 76 (23.7) | 64 (45.1) | 575 (38.2) |
| No education | 195 (20.7) | 138 (15.6) | 53 (49.5) | 150 (46.7) | 66 (46.5) | 755 (50.1) |
| missing | 998 (51.5) | 1358 (61.0) | 110 (50.7) | 513 (61.5) | 83 (36.9) | 992 (39.7) |
| **Health Zone / LGA / District**** | | | | | | |
| Kenge DRC / Fufore NG / Kole UG | 617 (31.8) | 883 (38.9) | 71 (32.7) | 309 (37.1) | 74 (32.9) | 618 (24.7) |
| Kingandu DRC / Mayo Belwa NG / Oyam UG | 503 (25.9) | 278 (12.3) | 123 (56.7) | 227 (27.2) | 119 (52.9) | 1399 (56.0) |
| Ipamu DRC / Song NG / Kwania UG | 819 (42.2) | 1108 (48.8) | 23 (10.6) | 298 (35.7) | 32 (14.2) | 482 (19.3) |

Number and column % of those with non-missing data, pooled, by country and by enrolment location; missing data rows are number and column %.

Abbreviations: DRC, Democratic Republic of the Congo; LGA, local government area; mRDT, malaria rapid diagnostic test; NG, Nigeria; RAS, rectal artesunate; RHF, referral health facility; UG, Uganda

* Severe malaria diagnosis was based on clinical assessment, diagnostic test result may or may not have been considered for the diagnosis

° At time of admission; DRC: October – April; Nigeria: May – October; Uganda: April – October

** Health zones in DRC (Kenge, Kingandu, Ipamu)/ LGA in Nigeria (Fufore, Mayo Belwa, Song) / District in Uganda (Kole, Oyam, Kwania)

***Table 5-2**: Administration of antimalarial treatment for severe malaria, by country and enrolment level*

| | DRC | | | Nigeria | | | Uganda | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Community enrolments** | **RHF enrolments** | ***P* value (Chi2)** | **Community enrolments** | **RHF enrolments** | ***P* value (Chi2)** | **Community enrolments** | **RHF enrolments** | ***P* value (Chi2)** |
| | **N = 1,939** n (%) | **N = 2,269** n (%) | | **N = 217** n (%) | **N= 834** n (%) | | **N = 225** n (%) | **N = 2,449** n (%) | |
| **Administration of at least one dose of an inj. antimalarial**[1] | 1613 (83.2) | 1908 (84.1) | 0.430 | 208 (95.9) | 776 (93.1) | 0.132 | 209 (92.9) | 2374 (95.0) | 0.171 |
| Artesunate | 1379 (71.1) | 1349 (59.5) | <0.001 | 202 (93.1) | 736 (88.3) | 0.040 | 201 (89.3) | 2286 (91.5) | 0.275 |
| Artemether | 11 (0.6) | 34 (1.5) | 0.003 | 6 (2.8) | 43 (5.2) | 0.137 | 0 (0.0) | 1 (0.0) | 0.764 |
| Quinine | 229 (11.8) | 539 (23.8) | <0.001 | 4 (1.8) | 8 (1.0) | 0.275 | 10 (4.4) | 99 (4.0) | 0.723 |
| **In-hospital administration of at least one dose of each an inj. and an oral antimalarial**[1] | 1300 (67.0) | 1499 (66.1) | 0.502 | 0 (0.0) | 28 (3.4) | 0.006 | 74 (32.9) | 1138 (45.5) | <0.001 |
| ACT[2] | 1100 (56.7) | 1017 (44.8) | <0.001 | 0 (0.0) | 28 (3.4) | 0.006 | 74 (32.9) | 1137 (45.5) | <0.001 |
| Artemether-lumefantrine[2] | 91 (4.7) | 91 (4.0) | 0.278 | 0 (0.0) | 27 (3.2) | 0.007 | 74 (32.9) | 1137 (45.5) | <0.001 |
| Artesunate-amodiaquine[2] | 1010 (52.1) | 930 (41.0) | <0.001 | 0 (0.0) | 1 (0.1) | 0.610 | 0 (0.0) | 0 (0.0) | NA |
| Quinine | 206 (10.6) | 494 (21.8) | <0.001 | 0 (0.0) | 0 (0.0) | NA | 0 (0.0) | 1 (0.0) | 0.764 |
| **Administration of ACT only** | 90 (4.6) | 57 (2.5) | <0.001 | 0 (0.0) | 4 (0.5) | 0.307 | 6 (2.7) | 65 (2.6) | 0.953 |

Number and column % of children receiving injectable and oral antimalarial treatment, pooled, by country and enrolment location.

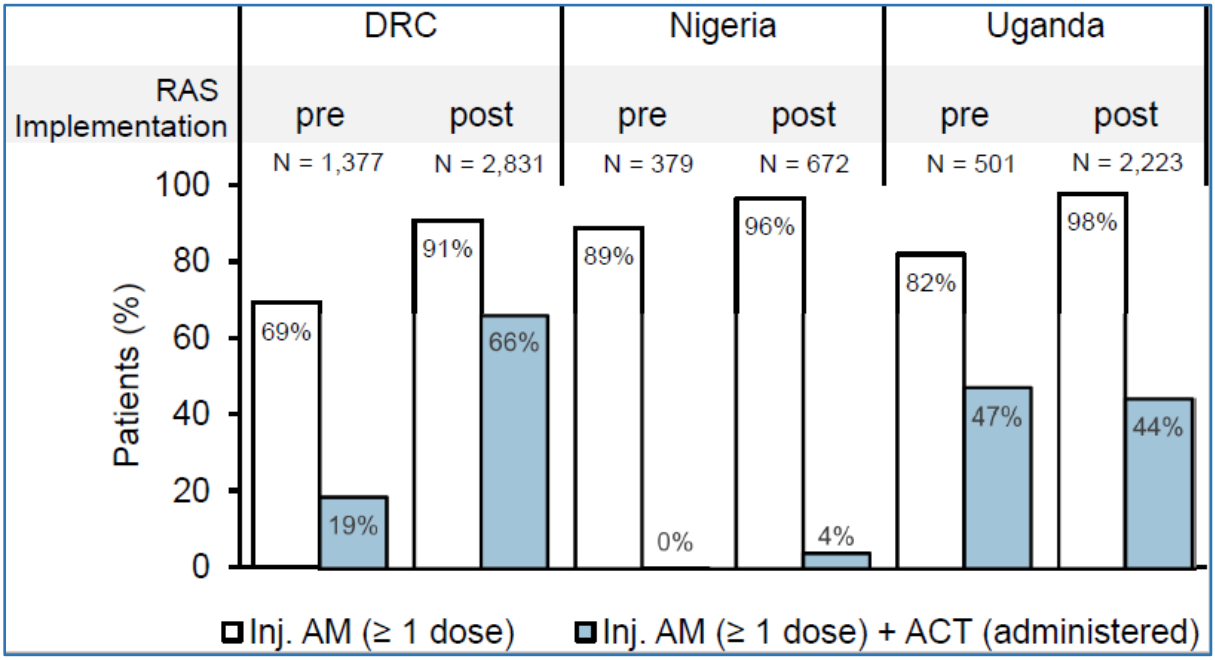
Abbreviations: ACT, artemisinin-based combination therapy; DRC, Democratic Republic of the Congo; RHF, referral health facility

[1] More than one type of antimalarial may have been administered

[2] Appropriate medication

**Fig 5–2. Appropriateness of antimalarial medication provided to children diagnosed with severe malaria before and after the implementation of RAS, by country and by enrolling provider (%).** Treatment of admitted children referred by a community-based provider or directly attending a RHF was assessed before and after the rollout of RAS (pre vs. post). Proportion of children administered at least one dose of an injectable antimalarial (artesunate, artemether or quinine; white bars) and at least one dose of an injectable antimalarial and an in-hospital ACT consisting of either artemether-lumefantrine (AL) or artesunate-amodiaquine (ASAQ). ACT, artemisinin-based combination therapy; AM, antimalarial; DRC, Democratic Republic of the Congo; RAS, rectal artesunate.

***Figure 5-2**: Appropriateness of antimalarial medication provided to children diagnosed with severe malaria before and after the implementation of RAS, by country and by enrolling provider (%)*



### ACT follow-on treatment

While only 2.7% (28/1,051) of the children in Nigeria received appropriate antimalarials during admission, i.e. an injectable and an ACT, 44.5% (1,211/2,724) did so in Uganda and 50.3% (2,117/4,208) in DRC (Table 5–2).

The pooled proportion of children receiving appropriate treatment increased significantly between the pre-implementation (21.9%, 494/2,257) and the post-implementation period (50.0%, 2,862/5,726, $P < 0.001$; Figure 5–2), mainly attributed to an increase of ACT administration among children treated with an injectable antimalarial observed in DRC (46.9 percentage points (258/1,377 pre- versus 1,859/2,831 post-implementation); $P < 0.001$) and Nigeria (3.8 percentage points (1/379 pre- versus 27/672 post-implementation); $P = 0.001$). Meanwhile, there was no difference of follow-on ACT use in Uganda.

### Predictors of appropriate antimalarial medication

While there was no difference in the odds of receiving appropriate antimalarials between community referrals and direct RHF attendances in Uganda and DRC (Table 5–3), community referrals in DRC were more likely to receive an injectable antimalarial followed by an ACT if they had received RAS pre-referral treatment in the post-implementation period (aOR = 2.13, 95% CI 1.55 - 2.92). In contrast, children in Uganda were less likely to be receiving an appropriate treatment if administered RAS (aOR = 0.37, 95% CI 0.14 - 0.96). The low numbers of community referrals and low levels of appropriate medication provision observed in Nigeria did not allow to compute estimates for these indicators.

In DRC, children admitted during the post-implementation period were much more likely to receive appropriate treatment compared to admissions during the pre-implementation phase (OR = 6.29, 95% CI 4.88 - 8.10). The odds for medication appropriateness were higher for children below 3 years (aOR = 1.45, 95% CI 1.19 - 1.77). No such differences were observed in the other two countries. Other predictors for appropriate antimalarial medication included whether costs were incurred to caregivers: Both in Uganda and DRC, payable hospitalization was positively correlated with receiving appropriate treatment, while the odds were lower if caregivers had to pay for medication. Again, the low number of events in Nigeria did not permit estimating these predictors. A sensitivity analysis using multiple imputation methods for weight showed on differences in the results (Supplementary Table 5–2).

***Table 5-3**: Patient, provider, caregiver and facility correlates with antimalarial medication appropriateness according to the WHO malaria treatment guidelines*

| | DRC | | Nigeria | | Uganda | |
|---|---|---|---|---|---|---|
| | **aOR (95% CI) [a]** | ***P* value** | **aOR (95% CI) [a]** | ***P* value** | **aOR (95% CI) [a]** | ***P* value** |
| **Patient variables** | | | | | | |
| **Age (years)** | | | | | | |
| < 1 | 1.45 (1.11 - 1.88) | 0.006 | 0.15 (0.01 - 1.68) | 0.12 | 1.01 (0.67 - 1.52) | 0.96 |
| 1 - 2 | 1.45 (1.19 - 1.77) | <0.001 | 0.72 (0.21 - 2.47) | 0.60 | 0.95 (0.72 - 1.27) | 0.74 |
| 3 - < 5 | Ref | | Ref | | Ref | |
| **Sex** | | | | | | |
| Male | Ref | | Ref | | Ref | |
| Female | 0.97 (0.84 - 1.12) | 0.65 | 0.41 (0.15 - 1.14) | 0.09 | 0.85 (0.69 - 1.05) | 0.13 |
| **Weight (kg)** | | | | | | |
| < 8 | 0.98 (0.75 - 1.30) | 0.91 | 1.99 (0.46 -8.68) | 0.36 | 1.36 (0.92 - 2.00) | 0.13 |
| 8 - 10 | 1.00 (0.83 - 1.21) | 0.98 | 1.30 (0.35 - 4.89) | 0.70 | 1.06 (0.82 - 1.39) | 0.65 |
| > 10 | Ref | | Ref | | Ref | |
| **Administration of RAS** | | | | | | |
| no (post-implementation, community) | Ref | | Ref | | Ref | |
| yes (post-implementation, community) | 2.13 (1.55 - 2.92) | <0.001 | 0.53 (0.01 - 9.02) | 0.95 | 0.37 (0.14 - 0.96) | 0.04 |
| NA (Pre-implementation, RHF) | 1.69 (1.10 - 2.60) | 0.02 | 2.79 (0.10 - 7.43) | 0.78 | 0.95 (0.32 - 2.79) | 0.93 |
| **Enrolment at community provider** | | | | | | |
| no | Ref | | Ref | | Ref | |
| yes | 1.15 (0.85 - 1.55) | 0.36 | 1.36 (0.15 – 4.76) | 0.86 | 1.57 (0.73 - 3.37) | 0.25 |
| **mRDT / blood slide result** | | | | | | |
| negative/not done | Ref | | Ref | | Ref | |
| positive | 1.00 (0.79 - 1.26) | 0.97 | 0.44 (0.17 - 1.14) | 0.09 | 2.32 (0.58 - 9.27) | 0.23 |
| **Provider variable** | | | | | | |
| **Costs incurred for** | | | | | | |
| Drugs | 0.81 (0.67 -0.97) | 0.02 | 1.01 (0.06 -14.3) | 0.82 | 0.24 (0.18 -0.33) | <0.001 |
| Hospitalization | 1.21 (1.02 -1.42) | 0.03 | 1.52 (0.12 -9.42) | 0.79 | 3.90 (2.77 -5.48) | <0.001 |
| **Caregiver variable** | | | | | | |
| **Age (Years)** | | | | | | |
| <30 | 1.17 (1.00 -1.38) | 0.05 | 0.53 (0.21 -1.37) | 0.19 | 1.20 (0.96 -1.49) | 0.12 |
| ≥30 | Ref | | Ref | | Ref | |
| **Other contextual factors** | | | | | | |
| **RAS implementation period (pre- vs. post-implementation)** | 6.29 (4.88 - 8.10) | <0.001 | 5.14 (0.57 - 46.4) | 0.15 | 1.03 (0.76 - 1.41) | 0.83 |
| **Health Zone / LGA / District◊** | | | | | | |
| Kenge DRC / Fufore NG / Kole UG | 1.18 (0.96 -1.44) | 0.07 | Ref | | Ref | |
| Kingandu DRC / Mayo Belwa NG / Oyam UG | 0.68 (0.55 -0.85) | <0.001 | 1.42 (0.42 - 16.4) | 0.78 | 6.71 (5.13 -8.77) | <0.001 |
| Ipamu DRC / Song NG / Kwania UG | Ref | | 8.28 (1.04 -65.9) | 0.05 | 1.84 (1.12 -3.03) | 0.02 |
| **Seasonality** (rainy season) | 1.03 (0.87 - 1.21) | 0.73 | 3.74 (0.74 - 18.8) | 0.11 | 0.66 (0.52 -0.86) | 0.002 |

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; DRC, Democratic Republic of the Congo; mRDT, malaria rapid diagnostic test; RAS, rectal artesunate

[a] adjusted Odds Ratios (aOR), 95% confidence intervals (CI) and p-value obtained from logistic models. Adjusted for covariates shown accounting for clustering at RHF level, participants with missing data for any of the variables were excluded

◊ Corresponds to Health zones in DRC (Kenge, Kingandu, Ipamu*) / LGA in Nigeria (Fufore*, Mayo Belwa, Song) / District in Uganda (Kole*, Oyam, Kwania) (* = Ref)

### In-hospital versus home ACT treatment

Study countries differed considerably in the way of providing follow-on ACT (Table 5–4). In DRC, ACT was usually started as an in-hospital therapy following completion of injectable treatment (78.7%, 1,314/1,669), and completed in 49.3% (822/1,669) of the cases while the patient was still hospitalized. By contrast, only 1.7% (7/421) in Nigeria and 45.7% (617/1,349) in Uganda received any ACTs as in-patients, as the usual process was to receive a prescription to buy an ACT at discharge: 54.4% (229/421) of admitted children in Nigeria, and 53.0 % (715/1,349) in Uganda.

### Antimalarial treatment compliance

Among the post-implementation subsample with detailed dosage information, the vast majority treated with an injectable antimalarial received at least three doses (3,220/3,337 (96.5%); Supplementary Table 5–3). In DRC, 76.2% (1,274/1,673) of children were treated with both an injectable and an ACT during admission (Figure 5–3), and including post-discharge prescriptions did not much change this percentage (76.9% (1,287/1,673); Table 5–4). As noted above for Nigeria in the full dataset analysis, the level of compliance of in-hospital treatment administration was very low (1.2%, 5/421); antimalarial prescription compliance was elevated but remained low at only 45.6% (192/421). In Uganda, including ACT prescriptions in the estimate for treatment compliance more than doubled the percentage (44.7% (606/1,355) vs. 97.5% (1,321/1,355), and compliance of in-hospital treatment administration to children referred from the community was lower as compared to direct RHF attendances (29.5% (39/132) vs. 46.4% (567/1,223), $P < 0.001$; Figure 5–3). Since community referrals were more likely to receive a prescription, this difference vanished for prescription compliance (98.5% (130/132) vs. 97.4% (1,191/1,223)).

**Figure 5–3. Antimalarial treatment compliance for children diagnosed with severe malaria after the implementation of RAS, by country and by enrolling provider (%).**
Antimalarial treatment administered in-hospital or prescribed at discharge to children referred by a CHW or PHC (C) or directly attending a RHF (R). A, Administration of at least 3 doses of an injectable antimalarial (artesunate, artemether or quinine). B, Administration of at least 3 doses of an injectable antimalarial and in-hospital follow-on ACT (light blue bars) or in-

hospital administered / at discharge prescribed / dispensed follow-on ACT (dark blue bars). Data collection period: Uganda and DRC: April 2019 - July 2020, Nigeria: May 2019 - July 2020. ACT, artemisinin-based combination therapy; AM, antimalarial; DRC, Democratic Republic of the Congo; RHF, Referral Health Facility; RAS, Rectal Artesunate; Rx, prescription.

***Table 5-4**: Provision of in-hospital vs. post-discharge ACT medication*

| | DRC | | | Nigeria | | | Uganda | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Community enrolments N = 846** n (%) | **RHF enrolments N = 823** n (%) | ***P* value (Chi2)** | **Community enrolments N = 113** n (%) | **RHF enrolments N = 308** n (%) | ***P* value (Chi2)** | **Community enrolments N = 132** n (%) | **RHF enrolments N = 1,217** n (%) | ***P* value (Chi2)** |
| **Provision of ACT treatment** | | | 0.021 | | | 0.200 | | | 0.002 |
| No ACT | 145 (17.1) | 170 (20.7) | | 54 (47.8) | 131 (42.5) | | 1 (0.8) | 15 (1.2) | |
| ACT treatment completed at facility * | 425 (50.2) | 397 (48.2) | | 0 (0.0) | 0 (0.0) | | 7 (5.3) | 165 (13.6) | |
| Started at facility, to be completed at home ◊ | 251 (29.7) | 241 (29.3) | | 0 (0.0) | 7 (2.3) | | 33 (25.0) | 412 (33.9) | |
| Received prescription to buy from pharmacy ° | 5 (0.6) | 9 (1.1) | | 59 (52.2) | 170 (55.2) | | 91 (68.9) | 624 (51.3) | |
| Other | 20 (2.4) | 6 (0.7) | | 0 (0.0) | 0 (0.0) | | 0 (0.0) | 1 (0.1) | |
| missing | 4 (0.5) | 0 (0.0) | | 0 (0.0) | 0 (0.0) | | 0 (0.0) | 6 (0.5) | |

Number and % of distribution of modalities of receiving ACT treatment, pooled, by country and enrolment location; missing data rows are number and column %.

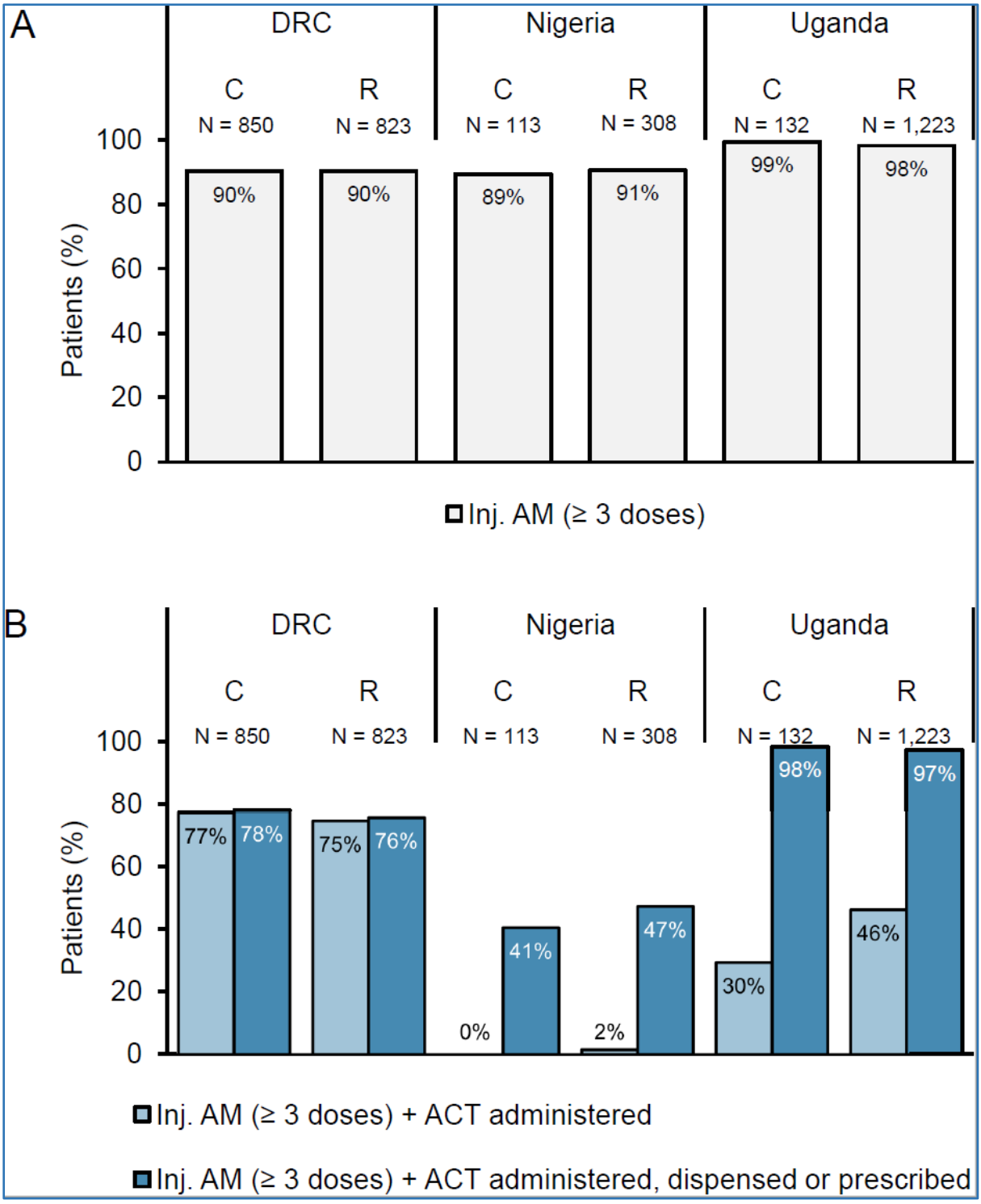
Abbreviations: ACT, artemisinin-based combination therapy; DRC, Democratic Republic of the Congo; RHF, referral health facility

* Includes 3 children who received artesunate + mefloquine

◊ Includes 7 children who received artesunate + mefloquine and 70 observations with missing specification of type of ACT given

° Includes 1 child who received a prescription for dihydroartemisinin + piperaquine and 37 observations with missing specification of type of ACT prescribed

***Figure 5-3**: Antimalarial treatment compliance for children diagnosed with severe malaria after the implementation of RAS, by country and by enrolling provider (%)*



## 5.5. Discussion

Pre-referral RAS administered in the community or at the PHC level is intended to rapidly initiate effective malaria treatment in hard-to-reach locations before the patient is referred to a health facility with full case management capabilities. Adequate post-referral management is critical to ensure complete patient cure and avoid death and persisting disability.

In line with previous studies (Achan *et al.* 2011, Shah *et al.* 2016, Zurovac *et al.* 2018, Ampadu *et al.* 2019), the majority of children treated for severe malaria at a RHF received an injectable antimalarial, usually artesunate. By contrast, our results show that completing a full course of an ACT (a central component of the WHO recommendation) is highly unsatisfactory. Published results for this indicator vary greatly between 4.8% in Uganda (Ampadu *et al.* 2019) and 43.4% in Nigeria (Ojo *et al.* 2020), though these reports do not specify whether ACTs were prescribed for in-hospital administration or at discharge. In our study, methods of ACT provision varied: ACTs were either directly administered at the RHF, or patients were discharged with a prescription for home treatment, or a variation thereof.

Our data suggest that in DRC and Uganda, a fair proportion of children start their ACT course while they are still admitted, likely being dispensed the remaining doses at discharge. This was rarely the case in Nigeria, where children either only received a prescription or no ACT at all. Failure to provide a full course of an ACT in the RHF and only giving a prescription raises two major concerns about the treatment's effectiveness. Firstly, an incomplete treatment together with a lower referral completion of community-enrolled children (Brunner *et al.* 2022), increases significantly the risk of an unfavorable health outcome, including the risk of dying. This may have contributed to our finding that the beneficial effect of pre-referral RAS on survival (Gomes *et al.* 2009, Okebe *et al.* 2014) could not be replicated in our "real-world" study settings (Hetzel *et al.* 2022). We also found a worrying level of sickness and mRDT positivity at day 28 among enrolled children; however, our study set-up did not permit distinguishing between new and recrudescent infections (Hetzel *et al.* 2022). Secondly, incomplete treatment results in artemisinin monotherapy (RAS and injectable artesunate) and a raised risk of artemisinin resistance development. The selection of *P. falciparum* harboring artemisinin K13 resistance mutations was found in the context of the CARAMAL project in Uganda (Awor et al., manuscript in preparation).

If treatment is provided as prescription, the patient's adherence is crucial to ensure effective antimalarial treatment. Studies on patient and caregiver adherence to antimalarial treatment guidelines found large variations among different countries, ranging from <50% to 100% (Ajayi *et al.* 2008, Banek *et al.* 2014, Bruxvoort *et al.* 2014, Siddiqui *et al.* 2015, Yakasai *et al.* 2015, Banek *et al.* 2018). Adherence was found to be influenced by whether ACTs were delivered by the public or the private sector, as well as by caregiver income (Yakasai *et al.* 2015). It seems likely, that adherence to ACT is higher if the drug is dispensed rather than provided as a prescription that needs to be filled by the caregiver.

Reason for discharging a child before the start of ACT therapy could include a limited bed capacity at RHFs, especially during rainy seasons or disease outbreaks; though a higher treatment compliance during the rainy season seen in Nigeria suggests otherwise (Table 5–3). COVID-19 restrictions in Nigeria and Uganda impacting people's movement and the supply chain between March and July 2020 likely affected the running of these facilities. ACT stock-outs at RHFs may also have led to an increase of prescriptions though our annual cross-sectional healthcare provider surveys did not reveal major stock-outs. Further, socioeconomic factors may have influenced differently hospitalization duration and treatment patterns among community and RHF enrolments. Such factors may account for our finding that referral cases in Uganda were more likely to receive a prescription rather than in-hospital ACT treatment compared to children directly attending a RHF. Early hospital discharge also happens if inpatient medical care is no longer required (e.g. the child is able to swallow and further treatment may be continued at home). Discharging therefore relieves the burden on both the RHF (beds) and the family (hospitalization costs).

The relatively high rate of treatment compliance observed in DRC during the post-implementation period may be a result of a number of supportive interventions implemented to facilitate the rollout and uptake of RAS (Lambiris *et al.* 2022, Lengeler *et al.* 2022). In particular, this included distributing injectable artesunate to RHFs to limit use of the inferior quinine (Dondorp *et al.* 2005, Dondorp *et al.* 2010, Conroy *et al.* 2021).

Administration of pre-referral RAS did have a positive impact on whether a child received appropriate treatment in DRC. This and increased use of injectable artesunate in referrals compared to RHF enrolments suggests an increased awareness and may be due to targeted health worker training in the frame of RAS rollout (Lengeler *et al.* 2022). In Uganda, RAS use was negatively correlated with appropriateness of antimalarial treatment. This finding raises important concerns, namely that the full course of antimalarial treatment for severe disease

may no longer be considered necessary by healthcare workers after a single dose of RAS and a rapid improvement of the child's episode. Our finding that the likelihood of receiving appropriate treatment increased if caregivers had to pay a hospitalization fee could imply the provision of better quality services if payment is made by patients.

This study was conducted in three countries with high malaria burden but very different health systems contexts which may, at least in part, explain the differences in treatment compliance observed. All 3 countries base their severe malaria treatment guidelines on the WHO recommendations. To comply with these guidelines, we identify the following prerequisites for provision of compliant treatment for severe malaria. First, as evidenced by our DRC data, availability of the recommended drugs, in particular artesunate and ACTs, must be guaranteed. Second, health workers must know and comply with the treatment guidelines; any incentives nor non-compliant treatment (e.g. financial) should be counteracted. Sensitization for the need to complete treatment even if symptoms have improved is of paramount importance. Third, if the ACT course cannot be completed at the RHF, drug dispensation seems more favorable than a prescription. Finally, mechanisms to monitor adherence of home treatment should be implemented to ensure adequate treatment completion (e.g. follow-up home visit by CHW).

While our study lacks detailed information on patient adherence with prescribed ACTs, the prospective recording of case management during admission provided more accurate information than other studies using a retrospective design. The present multi-country study allowed us to include an unprecedented large sample of severely ill children from very distinct contexts (in terms of disease burden, health system, access to healthcare, etc.) while investigating the effect of introducing pre-referral RAS.

At the same time, the surprisingly different contexts in each country led to different results for key parameters, and implied slight differences in the detail of data collected. This impacted negatively the depth in which certain findings could be analysed across countries. Information on caregiver socioeconomic parameters like education, employment status, income were not collected and could not be included as predictors in the regression model. Training of study staff and standardized record forms were implemented to minimize observer bias and differences between countries. We cannot rule out the possibility of a Hawthorne effect due to the study staff's presence, potentially leading to an overestimation of the quality of care.

Finally, this study was limited to evaluating the treatment of severe malaria based on the local clinicians' diagnosis of "severe malaria". This diagnosis was not independently confirmed

because it was neither possible nor desirable (to minimize the Hawthorne effect mentioned above) to place a fully qualified clinician in each RHF.

## 5.6. Conclusion

Pre-referral RAS for children in hard-to-reach locations can only be an effective addition to a functioning continuum of care for severe malaria, if post-referral treatment is adequate (Hetzel *et al.* 2022). While parenteral treatment was generally administered correctly and reliably, we found that the provision of ACTs to complete treatment was often not followed or left to the discretion of the caregiver for home treatment. This resulted in a low overall treatment compliance, entailing a danger of poor treatment outcomes and an increased risk of resistance development. In order to effectively integrate pre-referral RAS into the continuum of care for severe malaria, health system deficiencies need to be addressed and health worker compliance strengthened to ensure the provision of effective, life-saving post-referral treatment.

# 6. Health system readiness and the implementation of rectal artesunate for severe malaria in sub-Saharan Africa: an analysis of real-world costs and constraints

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## 6.1. Abstract


### Background

Rectal artesunate, an efficacious pre-referral treatment for severe malaria in children, was deployed at scale in Uganda, Nigeria and DR Congo. In addition to distributing rectal artesunate, implementation required additional investments in crucial but neglected components in the care for severe malaria. We examined the real-world costs and constraints to rectal artesunate implementation.

### Methods

We collected primary data on baseline health system constraints and subsequent rectal artesunate implementation expenditures. We calculated the equivalent annual cost of rectal artesunate implementation per child younger than 5 years at risk of severe malaria, from a health system perspective, separating neglected routine health system components from incremental costs of rectal artesunate RAS introduction.

### Findings

The largest baseline constraints were irregular health worker supervisions, inadequate referral facility worker training, and inadequate malaria commodity supplies. Health worker training and behaviour change campaigns were the largest startup costs, while supervision and supply chain management accounted for most annual routine costs. The equivalent annual costs of preparing the health system for managing severe malaria with RAS were US$2.63, $2.20 and $4.19 per child at risk and $322, $219 and $464 per child treated in Uganda, Nigeria and DR Congo. Strengthening the neglected, routine health system components accounted for the majority of these costs at 71.5%, 65.4% and 76.4% of per-child costs, respectively. Incremental rectal artesunate costs accounted for the minority remainder.

### Interpretation

Although rectal artesunate has been touted as a cost-effective pre-referral treatment for severe malaria in children, its real-world potential is limited by weak and under-financed health system components. Scaling up rectal artesunate or other interventions relying on community healthcare providers only makes sense alongside additional, essential health system investments sustained over the long-term.

## 6.2. Introduction

Of the estimated 400 000 annual malaria deaths, the majority are in children younger than 5 years living in Sub-Saharan Africa (WHO 2020). Without prompt treatment with parenteral artesunate followed by oral artemisinin-based combination therapy, an episode of severe malaria in children can rapidly lead to death (WHO 2015). Such comprehensive treatment presumes good access to higher-level healthcare facilities. Poor children living in remote, rural settings are challenged in accessing treatment and more likely to die from severe malaria (Karra *et al.* 2017, Coetzer *et al.* 2020).

Community Access to Rectal Artesunate for Malaria (CARAMAL) was an observational study accompanying the rollout of rectal artesunate, an efficacious pre-referral treatment for severe malaria, in highly endemic and difficult to reach rural settings in Uganda, Nigeria and the Democratic Republic of the Congo targeted to children younger than 5 years, under real world conditions. Rectal artesunate, a suppository, rapidly reduces parasite density and provides a child with severe malaria time to reach a referral health facility that can treat the illness appropriately. Before CARAMAL, one large randomized controlled trial found that rectal artesunate reduced severe malaria case fatality by 26% (relative risk 0.74; 95% CI [0.59-0.93]) (Gomes *et al.* 2009).

Rectal artesunate was delivered in rural communities via routine case management: community health workers (CHWs) trained on integrated community case management (iCCM) (Young *et al.* 2012), and peripheral healthcare facilities with no inpatient capacity. Implementation relied on appropriate training of health workers, supervision and a regular supply of drugs (Yeboah-Antwi *et al.* 2010, Smith Paintain *et al.* 2014, Vaughan *et al.* 2015). Since the successful treatment of severe malaria relies on a cascade of healthcare services from the community until post-referral treatment completion, the CARAMAL intervention funded both the introduction of rectal artesunate into community-level structures and some operational strengthening of existing routine systems along the continuum of care. This health system strengthening (HSS) included funding supervisions, some key supply chain inputs, and the training of referral facility workers on parenteral artesunate.

Although several studies have evaluated the costs of delivering services via CHWs (Collins *et al.* 2014, Vaughan *et al.* 2015, Daviaud *et al.* 2017, Escribano Ferrer *et al.* 2017) for a range of diseases, this is the first study, to our knowledge, that empirically assessed the real-world costs

of introducing rectal artesunate at community level, on a large scale, including strengthening neglected routine health system components.

Such real-world costs are not typically collected as part of randomized controlled trials, which are usually implemented under highly controlled conditions that often deviate from routine service delivery, and could plausibly underestimate true costs. In addition, we estimated the incremental cost of introducing rectal artesunate alone into an established system without additional HSS needs. In doing so, we documented important health system constraints, strategies implemented to overcome these, and their costs. The present analyses aim to inform operational guidance and financial planning in the replication or scale-up (Walker *et al.* 2002) of rectal artesunate as pre-referral treatment for severe malaria. The findings also provide economists and modelers with real-world parameter costs towards economic evaluations of comprehensive interventions for severe malaria.

## 6.3. Methods

### Implementation settings

The three settings differed markedly in the incidence of severe febrile episodes and the distribution of children per community-based provider and referral health facility (Table 6–1). The three settings were remote rural areas with high malaria endemicity and difficult access to higher-level care, including parenteral malaria treatment (see appendix 2 p 26 for maps), representative of areas of high malaria morbidity and mortality in sub-Saharan Africa. CHWs were unpaid volunteers and trained on iCCM–i.e. provision of treatment for malaria, pneumonia and diarrhoea. Uganda had the highest coverage of community-based providers (CHWs and peripheral healthcare facilities): national policy was that two CHWs be located in each village. In DRC and Nigeria, CHWs were strategically located in locations where other formal public health providers were considered hard-to-reach. An overview of the whole CARAMAL project can be found elsewhere (Lengeler *et al.* 2022). Briefly, the project aimed to test whether severe malaria fatality rates could be reduced by delivering rectal artesunate through established routine health systems, using a before-and-after plausibility design. The present manuscript deals with the costs of the programme.

The implementation of the CARAMAL project and the introduction of rectal artesunate took place between the fourth quarter of 2018 (Q4 2018) and Q4 2020 in Uganda, Nigeria and DR Congo. The intervention was implemented by local ministries of health supported by UNICEF (which we refer to as "implementers" throughout).

The CARAMAL study protocol was approved by the Research Ethics Review Committee of the World Health Organization (WHO ERC, ERC.0003008), the Ethics Committee of the University of Kinshasa School of Public Health (012/2018), the Health Research Ethics Committee of the Adamawa State Ministry of Health (S/MoH/1131/I), the National Health Research Ethics Committee of Nigeria (NHREC/01/01/2007-05/05/2018), the Higher Degrees, Research and Ethics Committee of the Makerere University School of Public Health (548), the Uganda National Council for Science and Technology (SS 4534), and the Scientific and Ethical Review Committee of Clinton Health Access Initiative (112, date Nov 21, 2017). The study was registered on ClinicalTrials.gov (NCT03568344).

**Scope of the evaluation**

Implementation activities were costed under a health system perspective and covered costs of services incurred by the Ministry of Health (MoH) to prepare the system to manage severe malaria with rectal artesunate. A community-based system prepared to manage sick children with suspected severe malaria included training health workers, an operational supervision system, adequate quantities of drug stock ordered and distributed and sufficient funding for behaviour change campaigns among other monitoring and evaluation activities. The perspective therefore excludes any incremental patient-level treatment costs of severe malaria and household costs (e.g. additional or reduced drug consumption due to behavioral changes in treatment-seeking patterns; transport) but includes the country's gross procurement of rectal artesunate and injectable artesunate, based on MoH stock orders (and not on actual drug units consumed), since possessing stock is a necessary condition for reaching readiness.

Full implementation costs are composed of two parts and labelled as either "startup" costs or annual recurring costs. Startup activities were one-time activities designed to launch the project. Recurring activities were routine activities underlying the functioning of the existing health system (e.g. iCCM), that recurred annually.

A year's worth of recurring activities was calculated from total expenditure per activity in the second year, per unit of time (quarters or number of months covered) before being converted to an annual cost.

We present these as economic costs expressed in real 2019 US dollars (for conversion methods see Appendix 2 p 28). Economic costs included level of effort costed via per-diems, time spent travelling and vehicle use, as well as donated commodities such as rectal artesunate and injectable artesunate adjusted to include cost, insurance and freight (Johns *et al.* 2003), using Global Fund prices (Global Fund 2021).

Research activities were excluded. Costs due to COVID-19 (e.g. personal protective equipment) were also excluded since they were purely incremental and did not change malaria-related costs.

In addition, we separated full implementation costs into HSS costs and incremental rectal artesunate-specific" costs. HSS costs refer to costs of routine activities of the health system related to severe malaria case management, which required improvement and funding support to meet the MoH guidelines (e.g. supervisions not occurring at recommended frequency, health workers at each level not receiving systematic refresher training, referral health facilities experiencing injectable artesunate stock outs etc.). We refer to these costs as system strengthening, rather than merely routine, to highlight that they either fully took over the funding of routine activities or complemented funding of essential, but often neglected, activities that national or donor financing was hitherto insufficient to cover. In contrast, rectal artesunate-specific costs were the incremental costs of introducing RAS into a health system with sufficient financing at baseline to operate in line with MoH guidelines. These rectal artesunate-specific costs included only activities that were additional to the aforementioned routine components of the health system. Rectal artesunate-specific costs included the proportion of training time judged specific to rectal artesunate; the procurement and distribution of rectal artesunate; the cost proportion of the initial behavioral change campaign, supervision or monitoring and evaluation relevant to rectal artesunate and severe malaria; and any novel elements that supported the introduction and maintenance of rectal artesunate that would not have been introduced otherwise. Expert opinion (UNICEF staff, including authors MM, FK, SL, MS, OO, EE, and VBu) decided these rectal artesunate-specific proportions. We calculated the rectal artesunate -specific costs for startup activities and annually recurring activities separately, and present them as shares of full implementation startup and recurring costs.

***Table 6-1**: Number of children younger than 5 years per healthcare provider and rate of severe febrile illness, by CARAMAL country*

| | **Uganda** | **Nigeria** | **DR Congo** |
|---|---|---|---|
| Implementation areas | Apac, Kole, Kwania and Oyam districts | Adamawa State – all local government areas in settings with active iCCM sites | Kenge, Ipamu and Kingandu health zones |
| Number of children (2019) | 259'681 | 188'897 | 149'671 |
| Number of children per community-based provider | 46 | 284 | 690 |
| Number of children per referral health facility | 11'816 | 55,022 | 7,045 |
| Rate of severe febrile illness per 1000 children | 14.9 | 5.3 | 16.9 |
| Community parasite rates in children | 53-78% | 38-61% | 40-57% |

Refers to children younger than 5 years in all cases. Numbers are drawn from CARAMAL patient surveillance system. Community-based healthcare providers include both community health workers and community healthcare facility workers. For details see (Lengeler *et al.* 2022). Note that implementation was carried out in a larger number of areas than those highlighted in (Lengeler *et al.* 2022) so the number of implementation areas and the number of children is larger in the present table. iCCM=integrated community case management.

Finally, we calculated two separate per-child costs: (1) the equivalent annual cost per child younger than 5 years at risk of severe malaria by dividing total equivalent annual cost by the total number of children younger than 5 years in the implementation areas (WorldPop 2021); and (2) the equivalent annual cost per child younger than 5 years treated with rectal artesunate. We obtained the equivalent annual cost by annualizing startup costs over 10 years, a time horizon reflecting longevity of a community-based programme (Daviaud *et al.* 2017) with recurring components (e.g. biannual refresher training) aimed at maintaining the programme over time (for formula see Appendix 2 p 29), before adding the annually recurring cost. We used a discount rate of 3% (Edejer *et al.* 2003).

As a secondary outcome, we estimated a proxy for the affordability of integrating rectal artesunate and HSS by comparing the public health expenditure per capita (World Bank 2021) with the recorded (non-discounted, non-annualized) implementation expenditures per capita. To obtain the latter we divided implementation startup costs and annual HSS costs by the total population in the study area. We then computed the ratio of implementation expenditures per capita to public health expenditures per capita.

**Implementation components**

We summarize the baseline country-specific health system constraints prior to the intervention and the main implementation components that were funded by CARAMAL in in Appendix 2 (pp 3–5). We also present the aims of each component and whether they solve a supply- or demand-side constraint (Vassall *et al.* 2016, Mikkelsen *et al.* 2017). A detailed account of baseline and intervention components, both recurring and startup, can be found in Appendix 2 (pp 6-13). In addition, we provide a narrative account of the intervention components in Appendix 2 (pp 30-31). Information on the baseline state of the health system was obtained from a survey of a stratified random sample of healthcare providers conducted in Q4 2018 and rapid readiness assessment of all referral health facilities in the CARAMAL study areas in Q4 2017 (Lengeler *et al.* 2022). Information on baseline supervisory and behavior change campaign activity, as well as funding gaps, was obtained from an interview with each local UNICEF implementation throughout the implementation period.

The main implementation components included training of CHWs, peripheral healthcare facility workers, and referral health facility workers, strengthening supervisions, procurement and supply chains, behaviour change campaigns, monitoring and evaluation and other supportive interventions. The distribution of rectal artesunate to communities was streamlined in a sustainable manner without creating a parallel supply chain for the project: CHWs were meant to restock rectal artesunate during supervisory visits. Under such circumstances, the absence of supervision implied rectal artesunate stock-outs. CARAMAL therefore covered the full costs of routine supervision (per-diems and travel expenses for supervisors or CHWs). To minimize commodity stock outs in the community, implementers in Uganda increased supervisory frequency from biannually to quarterly. In addition, parish coordinators were funded to restock rectal artesunate on a monthly basis since quarterly supervisions were not frequent enough to meet rectal artesunate demand (these were costed as an additional supply chain activity in Uganda). While systematic supervisions were a challenge in all countries, increasing their frequency was not necessary in DR Congo and Nigeria where they were supposed to occur on a monthly basis.

**Data**

Expenditure data provided by UNICEF was annual, between Q4 2018 and Q4 2020, and separate for Uganda, Nigeria and DR Congo. UNICEF determined the format expenditure data would be transferred to the research team in accordance with their institutional obligations. Total expenditures were divided into implementation activities, and further disaggregated into sub-activities for which a total expenditure was given by year. Additional items were added by the research team and completed via interviews with UNICEF staff aimed at obtaining in-depth understanding of activities and their purpose (sample expenditure table in appendix 2 p 14). Where co-funding from external donors was reported in annual reports or interviews, we did our best to obtain costs for these. Specifically, these included donations of injectable artesunate, rectal artesunate or co-funding of iCCM monitoring and evaluation systems. Relevant quantities such as number of rectal artesunate capsules procured or health workers trained were obtained from implementer interviews or CARAMAL annual reports. Analyses were done in R (4.2.2).

**Role of the funding source**

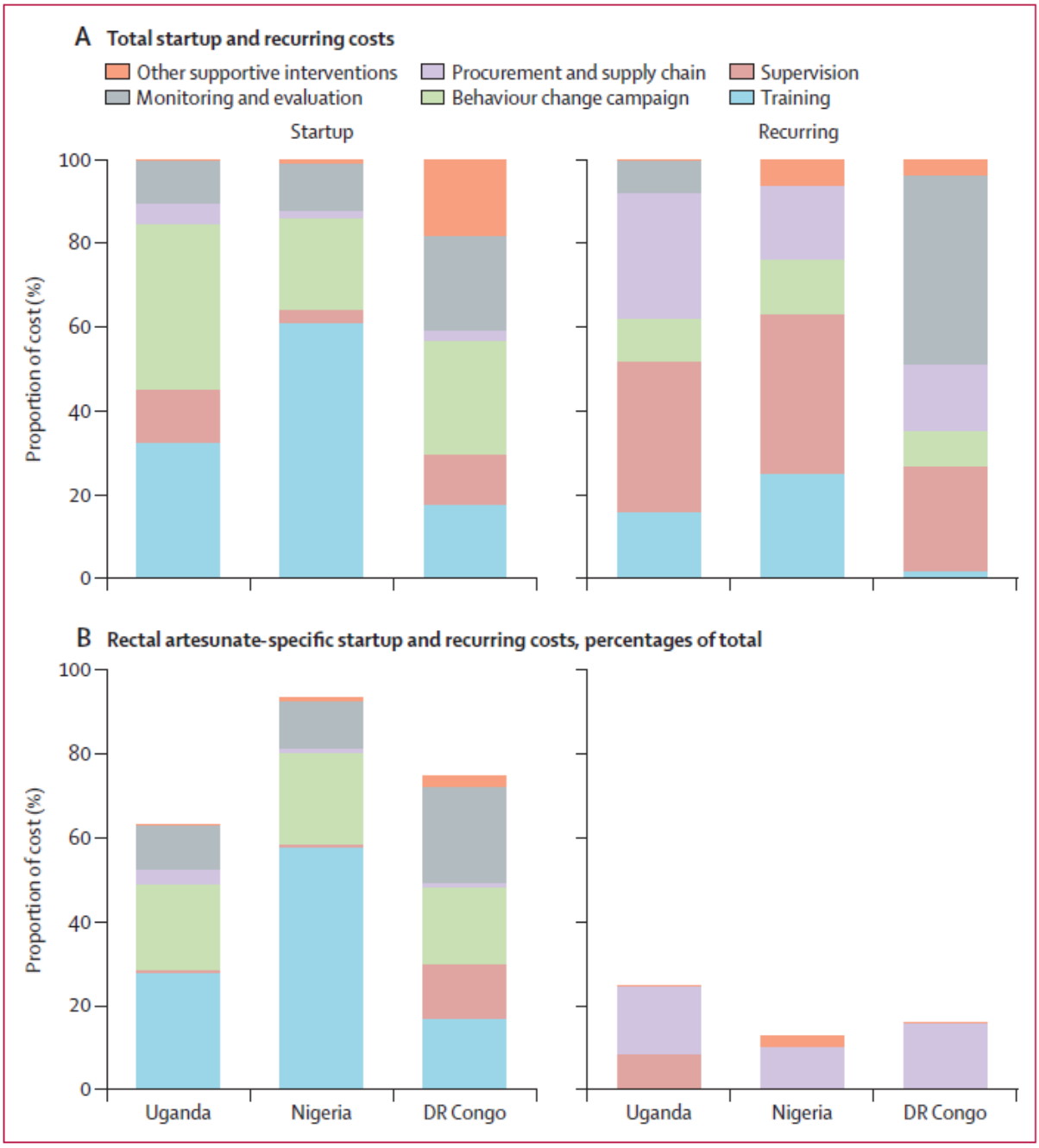
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

### 6.4. Results

Full startup costs in real 2019 US dollars were $613’304, $997’338 and $760’581 in Uganda, Nigeria and DR Congo, respectively. Annually recurring costs were $612'033, $301’554 and $540’601 in Uganda, Nigeria and DR Congo. We present programme component shares of full implementation costs in Figure 6-1A, separately for startup and annual HSS costs (see appendix 2 ppn6-13 for activity lists). Startup investments in health worker training accounted for large shares of full startup costs in the three countries. Training costs accounted for a greater share of startup costs in Nigeria relative to Uganda and DR Congo (61.2% vs 32.6% and 17.8% of startup costs respectively). The difference was due to transport and per-diems paid to Federal MoH officials (24% of total training costs) and the separate training programme for CHWs and peripheral healthcare facility workers in Nigeria, resulting in two sets of fixed costs (appendix 2 pp 8-10). We present training costs per CHW and peripheral healthcare facility worker in appendix 2 (p 15). In addition to training, large investments were made in behavior change campaigns. Behavior change campaigns BCC activities accounted for 39.6% of startup costs in Uganda, 22.12% in Nigeria and 27.1% in DR Congo. Investments in other supportive startup activities were made in DRC (19.3% of startup costs), mainly towards strengthening the quality of care for severe febrile illness at referral health facilities.

Supervisions were the largest component of annual HSS costs. Recurring supervision costs amounted to 36.0% of annual recurring costs in Uganda, 37.9% in Nigeria and 25.1% in DR Congo (Figure 6–1A). We provide annual supervision unit costs per CHW for Uganda and Nigeria in appendix 2 (p 15). Annual supply chain costs were 30%, 17.7% and 15.8% of annual recurring costs in Uganda, Nigeria and DR Congo, respectively. Apart from the procurement of rectal artesunate in each country, sub-components varied. Injectable artesunate was donated or procured and therefore costed annually. In Uganda, annual costs also included the monthly restocking of CHWs with RAS by parish coordinators (appendix 2 pp 6-13). We present monthly unit costs per CHW for these supportive interventions in appendix 2 (p 16). The large majority of costs went towards community and peripheral-level rather than referral-level activities (appendix 2 p 27).

***Figure 6-1**: Total and incremental rectal artesunate-specific startup and recurring costs, by programme component*




(A) Proportion of total intervention startup and recurring costs that each programme component accounted for.

(B) Rectal artesunate-specific proportion of the total presented in panel A. The proportions are calculated from total costs in real 2019 US dollars. Total startup costs were $613 304, $997 338, and $760 581 in Uganda, Nigeria, and DR Congo, respectively. Annually recurring costs were $612 033, $301 554, and $540 601 in Uganda, Nigeria, and DR Congo.

Figure 6–1B presents the share of full startup and annual recurring costs (i.e. the share of costs presented in Figure 6–1A), that are rectal artesunate-specific. Rectal artesunate-specific startup components in a functional and well-funded health system would cost 61.7%, 93.6% and 72.2%

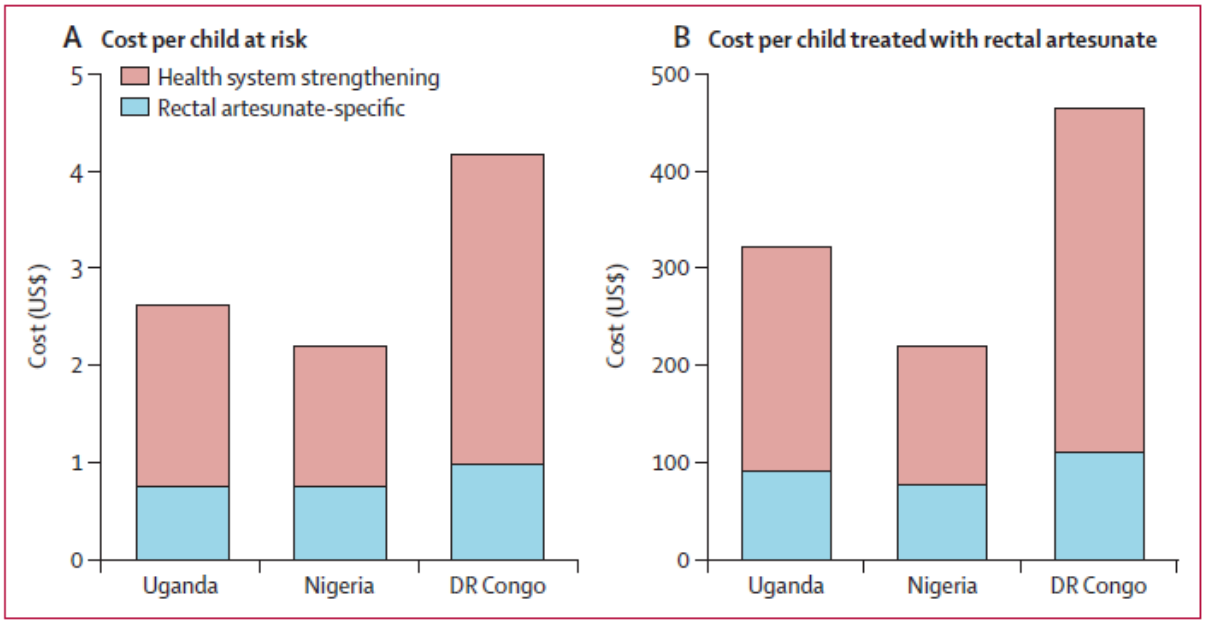
of actual startup costs in Uganda, Nigeria and DR Congo respectively (Figure 6–1B). Large initial health worker training costs (see appendix 2 pp 18-19 for sample schedule) and investments in behavior change campaigns accounted for the majority of the cost of setting up rectal artesunate within the community-based health systems. In DRC, supplementary and time-limited MoH supervisions were conducted for three months after the completion of training.

The required investment to maintain RAS post-startup in a system that already funds its community-based programmes sustainably can be seen in Figure 6–1B, right. RAS-specific annual costs are a fraction of total annual recurring costs at 24.7%, 13% and 16% in Uganda, Nigeria and DR Congo. As expected, the bulk of these activity costs are the procurement and the distribution of rectal artesunate to CHWs and peripheral healthcare facility workers. While these are similar shares in Nigeria and DR Congo, the share is higher in Uganda. As explained previously (Methods and appendix 2 pp 6-7), implementers rolled out specific interventions to ensure rectal artesunate was systematically distributed to the large number of CHWs (nearly twice the number of CHWs in Nigeria and more than 100 times that in DRC). The complementary proportions (75.3% in Uganda, 87% in Nigeria and 84% in DR Congo) represent the very large annually recurring HSS costs, necessary to maintain a functional community-based health system, regardless of rectal artesunate introduction.

We now turn to the economic costs per child younger than 5 years. The equivalent annual costs per child at risk of severe malaria were $2.63 in Uganda, $2.20 in Nigeria and $4.19 in DR Congo (Figure 6–2A). The costs for annual HSS made up the bulk of annual costs in all three project countries at $1.88, $1.44 and $3.20 in Uganda, Nigeria and DR Congo, respectively, with rectal artesunate-specific costs accounting for a minority at $0.75 in Uganda, $0.76 in Nigeria and $0.99 in DR Congo.

The equivalent annual costs per child younger than 5 years treated with rectal artesunate were $322 in Uganda, $219 in Nigeria and $464 in DR Congo (Figure 6–2B). HSS costs per child were $230, $143 and $354 in Uganda, Nigeria and DR Congo, while rectal artesunate-specific costs were $92, $76 and $110, respectively. We present absolute variation in startup, annually recurring and total costs per child at risk and per child treated in Table 6–2. (gross total costs and per-child costs by programme component as shown in appendix 2 pp 20-21; sensitivity analysis is presented in appendix 2 pp 22-23). Costs per child younger than 5 years are substantially higher in DR Congo than in Uganda or Nigeria due to the large financing requirements for monitoring and evaluation.

***Figure 6-2**: Health system strengthening versus rectal artesunate-specific equivalent annual cost of implementation, per child at risk of severe malaria and per child treated with rectal artesunate*




Refers to children younger than 5 years in all cases. Costs are calculated as equivalent annual costs and in 2019 real US dollars. Startup costs were annualized over 10 years. The denominator in panel A is the total number of children in implementation areas, or otherwise all children at risk of severe malaria. The number of children covered by the implementation in Nigeria was calculated as the total number of children in Adamawa State multiplied by the proportion of settlements in Adamawa covered by the integrated community case management programme (i.e., areas where the project was rolled out; 24·7%). The denominator in panel B was based on the total number of children recruited at the study sites either from a community health worker or a peripheral health-care facility (where, according to guidelines, a child with suspected severe malaria should be given rectal artesunate and referred; this assumes that once health system strengthening is sufficiently funded over the 10 year annualization period, rectal artesunate is stocked regularly and available). Since rectal artesunate was implemented in additional districts or local government areas in Uganda and Nigeria, compared with the areas where patients were enrolled, the number treated of children was scaled up proportionally. For the number of children treated with rectal artesunate see appendix 2 p 25 and Lengeler et al (2022) (Lengeler *et al.* 2022).

In proportions, HSS costs per child (regardless of which per-child cost we consider) accounted for 71.5% (Uganda), 65.4% (Nigeria) and 76.4% (DR Congo) of total annual implementations costs and rectal artesunate-specific costs per child younger than 5 years accounted for the minority at 28.5% (Uganda), 34.6% (Nigeria) and 23.6% of the full cost per child.

Expenditures (financial non-annualized, non-discounted costs) during the startup year (startup plus one year of HSS) amounted to 2.2%, 0.4% and 8.2% of the public health expenditure per capita in Uganda, Nigeria and DR Congo. For each year after that, HSS expenditures amounted to 1.1%, 0.1% and 4.1% of public health expenditures per capita.

The substantially lower affordability in DR Congo is driven by a significantly lower per capita health expenditure ($18.52 per capita) compared to Uganda ($43.14) and Nigeria ($83.75).

***Table 6-2:*** *Equivalent annual costs per child younger than 5 years at risk and treated*

| | **Equivalent Annual Cost per child at risk, US$** | | | **Equivalent Annual Cost per child treated, US$** | | |
|---|---|---|---|---|---|---|
| | **Start up** | **Recurrent** | **Total** | **Start up** | **Recurrent** | **Total** |
| **Uganda** | | | | | | |
| Training | 0.09 | 0.37 | 0.46 | 11 | 46 | 56 |
| Supervision | 0.03 | 0.85 | 0.88 | 4 | 104 | 108 |
| Behavioral Change Campaign | 0.11 | 0.24 | 0.35 | 13 | 30 | 43 |
| Procurement and supply chain | 0.01 | 0.71 | 0.72 | 2 | 86 | 88 |
| Monitoring and evaluation | 0.03 | 0.18 | 0.21 | 3 | 23 | 26 |
| Other supportive interventions | 0.00 | 0.00 | 0.00 | 0 | 0 | 0 |
| Total | 0.27 | 2.36 | 2.63 | 33 | 288 | 321 |
| **Nigeria** | | | | | | |
| Training | 0.37 | 0.40 | 0.77 | 37 | 40 | 77 |
| Supervision | 0.02 | 0.61 | 0.62 | 2 | 60 | 62 |
| Behavioral Change Campaign | 0.13 | 0.21 | 0.34 | 13 | 21 | 34 |
| Procurement and supply chain | 0.01 | 0.28 | 0.29 | 1 | 28 | 29 |
| Monitoring and evaluation | 0.07 | 0.00 | 0.07 | 7 | 0 | 7 |
| Other supportive interventions | 0.00 | 0.10 | 0.10 | 0 | 10 | 10 |
| Total | 0.60 | 1.60 | 2.20 | 60 | 159 | 219 |
| **DR Congo** | | | | | | |
| Training | 0.10 | 0.06 | 0.17 | 11 | 7 | 18 |
| Supervision | 0.07 | 0.91 | 0.98 | 8 | 100 | 108 |
| Behavioral Change Campaign | 0.16 | 0.31 | 0.47 | 17 | 35 | 52 |
| Procurement and supply chain | 0.01 | 0.57 | 0.59 | 1 | 63 | 65 |
| Monitoring and evaluation | 0.09 | 1.62 | 1.72 | 10 | 180 | 190 |
| Other supportive interventions | 0.10 | 0.13 | 0.24 | 12 | 15 | 26 |
| Total | 0.58 | 3.61 | 4.19 | 64 | 400 | 464 |

In some cases, the individual costs of each programme component do not sum exactly to the total due to rounding.

## 6.5. Discussion

CARAMAL introduced and monitored rectal artesunate in three distinct sub-Saharan African countries with high malaria burden, via community-level health-care providers. Implementation leveraged pre-existing community-level health infrastructure to deliver rectal artesunate in remote settings where access to health care was poor. It further strengthened core system components in the management of severe malaria. Training, supervision, the supply chain, behaviour change campaigns, monitoring and evaluation, and context-specific additional interventions were strengthened operationally and financially.

Using primary expenditure data and applying a health system perspective, we quantified the startup and annually recurring costs required to prepare community health systems for the effective management of suspected severe malaria cases in children younger than 5 years. The equivalent annual costs per child younger than 5 years at risk of severe malaria were $2·63 in Uganda, $2·20 in Nigeria, and $4·19 in DR Congo, while the costs per child treated with rectal artesunate were $322, $219, and $464, respectively. We also decomposed these full costs into the incremental cost of introducing rectal artesunate into the system, net of routine components, versus the HSS cost. The HSS components accounted for the largest share at 71·5% (Uganda), 65·4% (Nigeria), and 76·4% (DR Congo), with rectal artesunate-specific costs accounting for the minority remainder. Obviously, it would be considerably less costly to introduce rectal artesunate into settings where iCCM were already adequately financed and supply chains functional.

These costs are high and reflect low operational capacity and routine financing gaps, impeding the readiness of the health system to manage severe malaria from community to tertiary care level. Moreover, the health system constraints and the vast gaps in annual HSS financing should also be strong causes of concern for other, new interventions that aim to be delivered via community-based health-care systems (e.g. vaccines). Without ensuring adequate funding and strengthened operational capacity, the risk of failure remains high. Several other studies have encouraged the integration of health system constraints into costing as a crucial step towards realistic budgeting and cost-effectiveness analyses, across a range of diseases (Hanson *et al.* 2003, Vassall *et al.* 2016, Mikkelsen *et al.* 2017, Bozzani *et al.* 2018, Galactionova *et al.* 2020).

Due to CARAMAL's focus on severe disease and the health system constraints at different levels of the system, comparing our estimates with costs of other malaria interventions might be misleading. A review of the costs of CHW programmes in low-income and middle-income countries found only seven studies reporting these on malaria, with large heterogeneity in methods and scope (Vaughan *et al.* 2015). Among these, no studies focused on severe malaria exclusively. No studies to our knowledge included the cost of training and supervising community-based providers, which included peripheral health-care facilities, beyond merely CHWs, or the cost of preparing referral-level facilities with training and commodity provision for treating severe malaria. Additionally, while we adopted a health system perspective here, other studies included patient-level costs, with large estimated indirect costs. Although these societal perspectives are useful, they are beyond the present study's scope. In spite of these differences, our estimate of the CHW unit cost of training, a more commonly reported cost in other studies; lay within the broader range of other estimates in sub-Saharan Africa (Daviaud *et al.* 2017). Finally, it is important to stress that the investment made to prepare the health system for the management of severe malaria would also benefit the treatment of other common diseases covered by iCCM (WHO *et al.* 2012). For instance, regular training on managing drug stocks and submitting monthly drug reports as well as systematic supervisions of health workers are factors associated with the availability of drugs, such as amoxicillin to treat pneumonia and zinc and oral rehydration salts against diarrhoea (Bagonza *et al.* 2015). Subsequent cost-effectiveness analyses should include such benefits when trading them off against the large HSS costs.

While the above investments are necessary to prepare communities to fight against severe malaria, they are likely insufficient to truly overcome access barriers and save the lives of those in the poorest and most remote locations. CARAMAL did not identify a beneficial effect of rectal artesunate on child survival (Hetzel *et al.* 2022). Sick children must complete referral – which was often not the case (Brunner *et al.* 2022); and systematic post-referral treatment with artemisinin-based combination therapy must be guaranteed – which was also often not the case (Signorell *et al.* 2021).

Only then could RAS realize its full potential and more young lives be saved. Until then, RAS is unlikely to be cost-effective as has previously been claimed under controlled conditions (Tozan *et al.* 2010).

Finally, affordability of the intervention was substantially more favorable in Uganda and Nigeria than in DR Congo, where public health expenditures were the smallest.

The startup year amounted to 2%, 0.4% and 8.2% of the public health expenditure per capita in Uganda, Nigeria and DR Congo and 0.9%, 0.1% and 4.1% for every subsequent year after that. The DR Congo numbers are concerning considering that donor-driven contributions in DR Congo have dropped from 43% to 35% of total public health expenditures per capita between 2016 and 2018 at a time when total health expenditures per capita in DR Congo have decreased by $2 (World Bank 2021). More broadly, it remains a stark reality that many iCCM systems in Sub-Saharan Africa are largely dependent on donor funding (Rasanathan *et al.* 2014). Our study confirms that partial financing, often resulting from non-harmonized funding schemes (Malaria Consortium 2014), cannot sustain complex community health systems. Unless donor funding streams are aligned, harmonized and sustained over the long-run it seems unlikely that health system constraints, access to treatment, and reductions in malaria mortality will resolve.

We acknowledge several limitations to the paper. Firstly, reported costs are not purely incremental. In theory, some included activity costs, such as supervisions, should already have been covered by the health system but, in practice, were often not carried out prior to the intervention. It was, however, not possible to ascertain the exact proportion of failed supervisions. In such cases, CARAMAL financed the full activity instead of just the incremental proportion. This was particularly important for two reasons: (1) the lack of funding for supervision appears to be a persistent issue in iCCM and has been reported in other settings in Sub-Saharan Africa (Tavrow *et al.* 2002, Mathauer *et al.* 2006, Hill *et al.* 2014); and (2) overcoming constraints in supervisory activity operationally and financially also meant ensuring that rectal artesunate reached communities since supervisors often re-stocked CHWs directly. Second, while treatment level costs are beyond the scope of the analysis, RAS rollout might have knock-on effects and unintended consequences along the patient's continuum of care. Any changes in patient behaviour (e.g. reduced or increased referral completion) or health facility or drug utilization (e.g. fewer days of hospitalization) could additionally increase or reduce costs. A substantial proportion of these incremental costs (or cost savings) would likely be out-of-pocket patient costs and therefore require a broader, societal perspective, to be accurately assessed. Third, while we have conducted sensitivity analysis, the level of aggregation of our data did not allow for measuring within-setting variation in costs. Finally, while rectal artesunate-specific costs seems to be quite similar across settings, the bulk of the total costs are driven by setting-specific health system constraints.

A number of these are shared across settings (e.g. lack of funding for supervisions, stock outs etc.); others however are not. Therefore, caution should be used when generalizing these costs to other settings that may differ in the constraints they face, to avoid over- or likely under-estimating true costs.

# 7. General discussion

The present thesis aimed to determine challenges and to assess key interventions for the responsible introduction of rectal artesunate into the DRC health system, as a pre-referral treatment for suspected severe malaria cases at the community level. Thus, it aimed to support the strategic planning of malaria control in the DRC, the second most malarious country in the world. Our approach was to understand specifically the use of RAS as part of the continuum of care for suspected severe malaria cases, from the community level to referral health facilities. As CARAMAL came to its conclusion at the end of 2021, much remains to be done in terms of optimizing RAS for its use under real-world situations, and more generally in optimizing the management of severely ill children. While many studies have focused on the acceptability of RAS (Phiri *et al.* 2016, Mvumbi *et al.* 2019, Angus 2020), few studies to date have investigated and documented its operational use, and none on any large scale. In addition, much remains to be done in understanding the burden of severe fever diseases at community level. Obviously, dealing with severely ill children with a high risk of dying is of very high priority for reducing the unacceptably high mortality in Congolese children. The DRC has ordered several thousand units of RAS through the ongoing Global Fund grant (2021-2023), and there was much pressure from the government and from donors to implement this intervention. Hence, it was urgent to clarify its rational use with reliable national field data. The present thesis constituted the opportunity to generate strong operational evidence for the rational and responsible introduction of RAS.

In Chapter 3, we described the distribution of severity signs and symptoms among children <5 years with an episode of severe febrile illness/suspected SM. We also assessed the predictive value of a number of danger signs and symptoms on key study outcomes: likelihood of RAS use, referral completion, administration of injectable artesunate in a RHF, and health outcomes including clinical cure and mortality. Our findings showed that approximately three-quarters of patients had iCCM general danger signs. An age of 2-5 years and iCCM general danger signs predicted positively RAS use, and RAS administration positively affected referral completion. While RAS did not seem to reduce significantly the CRF at Day 28, it improved at least the health status of the children. Importantly, a full severe malaria treatment at the RHF including an injectable anti-malarial and a full course of an ACT was highly protective against death.

The work completed in chapter 4 aimed to determine the prevalence of malaria infections and anaemia in children under 5 years of age at community level in three Health Zones in the DRC,

and assess the level of caregiver's knowledge and attitudes towards malaria and pre-referral RAS. It also investigated determinants of caregiver's treatment seeking patterns and decision-making. These are essential elements in understanding the real-world effectiveness of this seemingly simple intervention when used in a complex health care and social system. Hence, the findings can hopefully be used to optimize its implementation at large scale in settings with limited resources. Our findings suggest that caregiver's recognition of severe malaria signs was poor, while knowledge of symptoms of uncomplicated malaria appeared to be high. Despite this, danger signs significantly increased the odds of seeking treatment. Conversely, "doing something at home" against fever negatively affected treatment seeking, presumably, because there was a sense among the caretakers that something was being done and no further action was required. Malaria prevalence (59.8%) and anaemia (≥79%) in the community were high compared to other findings from the DRC: overall 31% (DHS-DRC 2014) and 38.5% (INS 2019), and 6.9% for anaemia at the threshold of Hb<8.0g/dL (INS 2019). A lower prevalence of malaria (ranging from 14.1% to 38%) was also found in Kinshasa and other settings of the DRC (Ferrari *et al.* 2016, Emina *et al.* 2021).

In Chapter 5, we assessed health worker compliance with severe malaria treatment guidelines in the context of implementing pre-referral RAS. Antimalarial treatment was assessed for children referred from a community-based provider, as well as for those directly attending the RHF. Our findings showed that only about half of the admitted children were administered both a parenteral antimalarial and an ACT in DRC. While low, this proportion was still higher than in the other two CARAMAL countries Uganda and Nigeria. Children receiving RAS from a community-based provider were more likely to be administered the full post-referral medication in DRC compared to Nigeria and Uganda. While in DRC in-patient ACT administration was common, ACTs were often only prescribed at discharge in Nigeria and Uganda, with a resulting low treatment compliance. This bore a high risk of incomplete treatment because of partial parasite clearance and disease recrudescence. In other words, health care providers in RHFs in the three countries did often not comply with both WHO and essential national treatment guidelines.

In Chapter 6, we empirically assessed the real world costs of introducing RAS on a large scale at community-level, including some limited strengthening of routine health system components. We also estimated the incremental cost of introducing RAS alone into an established system without additional "health system strengthening" (HSS). Our analyses aimed to inform operational guidance and financial planning in view of the national scale-up

of RAS as pre-referral treatment for severe malaria. Lastly, the findings should also provide economists and modelers with real-world parameter costs for economic evaluations of interventions for severe malaria. Our findings showed that health worker training and behaviour change campaigns were the largest startup costs, while supervision and supply chain management accounted for most of the annual routine costs.

In the discussion below, we focused on the DRC situation, despite the fact that two of the four papers included in this dissertation presented also results for the other two CARAMAL countries.

## 7.1. Implications for treatment seeking and suspected severe malaria case management at community level

### 7.1.1. Implications for treatment seeking

Treatment seeking is the starting point for the case management process and the use of pre-referral RAS in CHCS and PHCs. It is affected by factors such as the level of information on a given disease, knowledge, culture and customs of potential users. In DRC, only CHCS and PHCs are allowed to treat suspected severe malaria in children aged 6 months to <6 years with pre-referral RAS (NMCP 2021).

Despite a fairly good knowledge of mild malaria symptoms and treatment, severe malaria signs (danger signs) are rather less well known. According to the iCCM guidelines, four dangers signs are indicative of severe malaria and hence should trigger RAS administration: vomiting everything, convulsions, not being able to drink/eat, and being very sleepy or even unconscious (WHO 2012). Of these, only convulsions and "vomiting everything" seemed to be known by 4/10 of caregivers interviewed during household surveys. Ignorance of the recognition of danger signs by the majority of caregivers is obviously of concern, since this could reduce care seeking from a health provider, where they child can be given RAS.

When planning for RAS scale-up. It is therefore critical to spread effective key messages, including danger signs and "good" attitudes to adopt in case of symptoms. The key message to convey must be short, clear, concise, in local languages and suitable for the intended audience, although having received information was not found to be the sole determinant of knowledge (Ntamabyaliro *et al.* 2021).

Different channels may be used to ensure an effective delivery of key messages to a broad audience constituted by individuals among which nearly one third attended only primary school or had no education at all. Firstly, radios are owned by 26.8% of households in rural areas (INS 2019), where access to other media is still very limited. Radio has been shown to be an effective channel to spread malaria related knowledge (Ntamabyaliro *et al.* 2021). Secondly, SMS alerts through mobile phones could be used, since phones are owned by nearly half (49.9%) of Congolese adults (Target 2021). Thirdly, trained CHWs might also help spreading messages during their home visits. Their effectiveness in such a context has been demonstrated for example in Zambia, where trained CHWs are sensitizing communities on how to prevent and treat malaria. As a result, malaria has reached record low levels in the parts of Zambia that is now aiming towards a malaria-free future (PATH 2019). In the DRC, this constitutes a way of capitalizing on the so-called "promotional" CHWs, while the "provider" CHWs can concentrate on treating patients. Lastly, churches might also play an important role, as their influence on malaria control practices has been demonstrated elsewhere in African (Maigemu *et al.* 2015). Since 95% of the Congolese population is Christian (ARDA 2020), churches might be a suitable place where such messages can be conveyed to a broad audience. All of the above channels have the advantage of being inexpensive and requiring little time to implement. On the other hand, it is essential to ensure the long-term sustainability of the imparted knowledge through intensive health education programs (Hetzel *et al.* 2008). Such programs have been successfully implemented in Tanzania, even though they are much more expensive and time consuming.

CHW's services are free of charge, but this appears not to be enough to improve patient attendance. Recurrent and long-term stock-outs of essential drugs do contribute as well to poor attendance, as evidenced by findings from several studies. One such study found that the availability of quality medicines in the provision of healthcare services is an important part of universal health coverage, shaping health services delivery and household healthcare utilization (Kuwawenaruwa *et al.* 2020). Other studies showed that stock-out of medicines negatively affects treatment seeking in community-based health providers (Das *et al.* 2010, Olaniran *et al.* 2022).

Therefore, better supporting the supply of essential medicines and other commodities in CHCS and PHCs is likely to be a strong incentive for attendance, and thus would also increasing the demand for RAS.

In the DRC, the number of CHCS in service remains very low. Of an estimated 18,350 CHCS that would be required (Severe Malaria Observatory 2022), only half (9,349) were functional in 2021. The country's current efforts to develop that cadre should be maintained, and it added 1,921 new CHCS in 2021 (PNECHOL-MD 2022). Increasing the number of CHCs and CHWs will ultimately improve health coverage, especially for the rural populations.

### 7.1.2. Implications for suspected severe malaria case management at community level

The management of suspected severe malaria cases involves several components, including the health care providers, guidelines, drugs and other supplies. The primary health care provider (CHW / nurse in PHC) is the main actor. Using his/her knowledge, the provider is responsible for patient assessment and s/he should adhere to existing guidelines.

It is of great importance to plan regular trainings for health care workers, focusing on clinical practice relevant for their daily work, instead of administrative matters. In addition, the operational level should be trained by the nearest hierarchical level, in a decentralized perspective for greater efficiency (Lambiris *et al.* 2022). This might consist of training PHC nurses by health zone representatives, and then CHWs by these nurses.

According to the current DRC guidance, only CHW and PHC are allowed to provide pre-referral RAS to children aged 6 months to <6 years with fever or recent history of fever and at least one iCCM danger sign (WHO *et al.* 2012, NMCP 2021). In practice, however, RAS is also given to children presenting one of the following additional danger signs: unable to sit or stand up, as well as asthenia (Okitawutshu *et al.* 2022). This is not congruent with the global definition of iCCM danger signs (WHO 2011, WHO 2012).

In addition to this, we observed non-adherence of providers to the guidelines. As contribution to overall quality of care, it is important to update and harmonize the current DRC definition of iCCM danger signs and malaria guidelines with the global iCCM algorithms and WHO recommendations. Following this, health providers' trainings on the harmonized versions is crucial to ensure their adherence.

A critical and open question remains what to do when a community-based health provider has given RAS to an eligible child, but referral is either not possible or refused by the caregiver. Since this scenario is rather frequent, realistic ways of dealing with the situation should be sought, for example by slightly increasing local treatment options. Pursuing the treatment with additional RAS doses could for example lead to some children returning to a better health status

and therefore be managed entirely at the primary level. It is important to re-state that the presence of danger signs according to iCCM guidelines does not necessarily mean severe malaria. Either they are mild malaria episodes with a single transient danger sign, or the children have another truly severe non-malarial disease, for example sepsis (White 2022) or pneumonia (UNICEF 2022).

For such conditions, several studies conducted in the DRC and elsewhere demonstrated the efficacy of alternative antibiotic regimens for the treatment of possible severe bacterial infections in outpatients when referral is not possible (Baqui *et al.* 2015, Tshefu *et al.* 2015, Tshefu *et al.* 2015). The feasibility of such a strategy was shown in the DRC (Lokangaka *et al.* 2022). It would be therefore very interesting to initiate a combined early treatment made of RAS and of a broad-spectrum antibiotic for severe malaria fevers that cannot be diagnosed formally at the primary care level. Unfortunately, no suppositories combining both drugs are available, but their development should be considered urgently.

Finally, RAS offers now an opportunity for switching from the use of IM artesunate or IM artemether to definitive treatment of severe malaria at PHCs. In terms of their training, nurses at PHCs are similar to their colleagues at RHFs and could presumably manage more severe cases. This is actually seen in some RHFs that are actually being led by nurses who manage severe cases. Hence, with adequate training and a minimum provision of additional facilities including beds, PHCs could provide definitive treatment of many forms of severe malaria in areas that are hard-to-reach (Adesoro *et al.* 2016, Kefyalew *et al.* 2016). There are, however, also major clinical presentations of severe malaria that are associated with a high mortality risk including coma, respiratory distress (acidosis) and severe anaemia (English *et al.* 1996, von Seidlein *et al.* 2012); these must be transferred to a higher-level of care for comprehensive management (White 2022).

## 7.2. Implications for referral completion of suspected severe malaria cases at higher level of care

As noted above, in DRC about 1/3 of children that were given RAS did not complete referral to a dedicated RHF (Brunner *et al.* 2022), where they would be expected to receive comprehensive care for severe malaria.

Factors associated with less referral completion included age (the older the less), attendance at a CHW, location (HZ), and those unable to sit (Okitawutshu *et al.* 2022). Other factors were found elsewhere including receiving RAS, lack of money, cost of care, lacking means of transport, and big distances (Simba *et al.* 2010, Lal *et al.* 2018, Brunner *et al.* 2022).

The private health care sector, accounting for more than 40% of health facilities in the DRC plays unfortunately also a negative role in referral outcomes.

Thus, a holistic approach to improve referral completion in the context of pre-referral RAS scaling-up should be considered. Car ambulance would be the best option, but they are costly to acquire and maintain. "Moto ambulance" have been successfully tested in several rural HZ in the former Bandundu Province. Motorbikes can be used successfully in remote areas with poor roads. They are also cheaper and are often available already as taxis.

### 7.3. Implications for severe malaria case management in referral health facilities

RAS is meant to be an effective part of the continuum of care starting at peripheral level and leading to a higher-level of care (RHF) equipped for inpatient care of severe malaria (WHO 2012). In the DRC health system, RHFs are made of referral health centers and general referral hospitals. According to WHO guidelines and country policy, only RHF are allowed to provide comprehensive treatment of severe malaria with injectable artesunate followed by an 3-day full course of an oral ACT (NMCP 2021, WHO 2022). In addition, RHFs should be capable of providing supportive care such as blood transfusions for severe anaemia, oxygen in respiratory distress, and intubation in coma (cerebral malaria). In reality, this capability is often not in place in many RHFs. Blood banks and oxygen are rare. The availability of injectable artesunate and ACTs also remains problematic, as stock-outs are common. As a result, almost half of children with severe malaria are still being treated with quinine (Ntamabyaliro *et al.* 2018, Signorell *et al.* 2021), which is rarely out of stock (KSPH 2019).

The stock-outs of injectable artesunate could be explained in part by an underestimation of the needs, since calculations mainly consider children under the age of 5, while other age groups are also in need of the drug. The non-rational use in the treatment of uncomplicated malaria, the complex nature of the supply chain, as well as logistics challenges also increase the stock-out likelihood. When introducing pre-referral RAS, the need for injectable artesunate is

expected to increase, and a successful pre-referral RAS scale-up should obviously account for this.

Severe anaemia, one of the three main clinical presentations of severe malaria (Taylor *et al.* 2006, von Seidlein *et al.* 2012, WHO 2014) is a major contributor of malaria related deaths in the DRC. Although RAS rapidly reduces parasitaemia (Gomes *et al.* 2008), it does not eliminate all parasites and especially it does not treat severe anaemia. Only blood transfusions can save lives in the case of very severe anaemia, but the lack of blood banks in rural DRC is a real problem. Of 19 RHF covered by the CARAMAL project in the DRC (Lengeler *et al.* 2022), only one had a functioning blood bank, while more than one-third of severe malaria cases had severe anaemia (Okitawutshu *et al.* 2022). In addition, the cost of a blood transfusion is prohibitive for many patients (Lambiris *et al.* 2022). This problem needs addressing urgently.

As was shown in this thesis, the provision of a full treatment of severe malaria including an injectable treatment followed by a fully course of an ACT is crucial and likely to save many lives (Okitawutshu *et al.* 2022). However, only 50.3% of CARAMAL patients were administered such a full treatment of severe malaria in RHFs (Signorell *et al.* 2021), and this figure would have been substantially lower without the project supplying injectable artesunate where required. Finally, RAS followed of not by parenteral artesunate and not followed up with an oral ACT constitutes an artemisinin monotherapy that may favor the selection of resistant parasites (Aydemir *et al.* 2018, Deutsch-Feldman *et al.* 2019, Signorell *et al.* 2021).

### 7.4. Implications for the scale-up of rectal artesunate use

The efficacy of RAS against malaria parasite is undisputed (Karunajeewa *et al.* 2007, Sinclair *et al.* 2012). The biological mechanism through which pre-referral RAS can save time for a child with severe malaria to reach a higher-level health care facility for comprehensive treatment is plausible, based on a large multi-centre randomized controlled trial (RCT) (Gomes *et al.* 2009). Unfortunately, the experience from the CARAMAL project showed that contrary to the RCT data, the effectiveness of RAS is low in weak health systems (Hetzel *et al.* 2022). Since RAS requires a functioning health system capable of delivering all the component of care, it is critical to invest first in the strengthening of the health system prior a large scale up of RAS. This can be a major investment, but one that is absolutely necessary and which will bear many other positive externalities. Unless this is done, RAS is unlikely to be able to deploy its full child-saving potential.

# 8. Overall conclusions and outlook

In conclusion, this thesis has comprehensively identified the operational challenges encountered in the management of severe malaria cases in the DRC health system, from the community level to a referral level of care. It has summarized lessons learned for the rational and responsible introduction of pre-referral RAS in the DRC. Although RAS was shown in controlled conditions to be an effective treatment for malaria, being fast acting and safe, its potential effectiveness as life-saving pre-referral intervention under real-world conditions could not be confirmed. We identified many shortcomings in the case management of severely ill children, and confirmed that RAS can only perform as expected once the entire case management continuum is operating at a satisfactory level. Therefore, the successful implementation of RAS at a large scale in the DRC requires a comprehensive health system audit and a strengthening of its key functions. These include among others: (1) referrals, (2) the quality and availability of the post-referral treatment including diagnosis, injectable artesunate and an ACT. Key functions also include blood transfusions, oxygen and other supportive treatments. The possibility to decentralize severe malaria case management to the primary level could contribute to reducing child death from severe malaria and should be urgently investigated. For example in the form of a randomized controlled trial comparing the current systematic referral procedures to a more decentralized approach. It is also necessary to provide regular trainings and re-trainings of health providers at all levels to improve compliance with all treatment guidelines. Lastly, improving caregiver's knowledge of malaria and more generally danger signs is crucial for optimizing the chances of children to survive to adulthood under the best conditions possible.

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Zurovac, D., B. Machini, R. Kiptui, D. Memusi, B. Amboko, S. Kigen, P. Njiri and E. Waqo (2018). "Monitoring health systems readiness and inpatient malaria case-management at Kenyan county hospitals." Malar J **17**(1): 213.

# 10. Appendix – Curriculum vitae


| | |
|---|---|
| Full name | Jean Okitawutshu Djemba |
| Address | Byfangweg 6, 4051 Basel, Switzerland |
| Phone | +41 779 996 121; +243 818 381 364; +243 972 676 507 |
| Email address | jean.okitawutshu@swisstph.ch, jeanokitawutshu@gmail.com |
| Place, date of birth | Oduku (DRC), 18 August 1980 |
| Citizenship | Congolese (DRC) |
| Marital status | Married, 1 child |


**Education**

| | |
|---|---|
| 2019- | Ph.D. in Epidemiology and Public Health, Swiss Tropical and Public Health Institute, University of Basel, Switzerland |
| 2014-2015 | MPH, Master of Public Health, Health and Development orientation, Free University of Brussels (ULB), Brussels, Belgium |
| 2006-2010 | M.D. Notre-Dame University of Kasayi, Kananga, DRC |
| 2003-2006 | Diploma in Biomedical Sciences, Notre-Dame University of Kasayi, Kananga, DRC |

**Language skills**

Lingala (Native speaker)
Otetela (Native speaker)
French (Native speaker)
English (Fluent)

**Professional membership**

| | |
|---|---|
| 2018- | American Society of Tropical Medicine and Hygiene |

**Positions and scientific Appointments**

| | |
|---|---|
| 2019- | Teaching Assistant, Kinshasa School of Public Health, University of Kinshasa, DRC. |
| Oct. 2017-Nov. 2021 | Senior Scientist & Study Coordinator. The Community Access to Rectal Artesunate for Malaria (CARAMAL) in DRC.<br>This was a large-scale operational pilot study in three African malaria-endemic settings including the DRC, Nigeria and Uganda, to provide evidence of the real-life public health value of rectal artesunate (RAS). The project also aimed to assess health care seeking patterns, severe malaria case management at community and referral facility levels and describing RAS use and acceptance. |
| Mar. 2016-Jul. 2017 | Assistant Study Coordinator. The Demonstration Site of delivering simplified antibiotic regimens to young infants with possible severe bacterial infection where referral is not possible: an implementation study research in North and South Ubangi Provinces, DRC. |

| | |
|---|---|
| | The objective was to document the feasibility of delivering simplified antibiotic regimen out of research settings. |
| Aug. 2015-<br>June 2017 | Study Coordinator. Aspirin Supplementation for Pregnancy-Indicated Risk Reduction in Nulliparous Women (ASPIRIN): a randomized, double blind, placebo-controlled trial. North and South Ubangi Provinces, DRC. |
| Mar. 2014-<br>Sep. 2014 | Field Supervisor. Preconception Maternal Nutrition (Women First Study). North and South Ubangi Provinces, DRC.<br>The primary objective of the study was to determine the benefits to the offspring of woman in poor, food-insecure environment of commencing a daily comprehensive maternal nutrition supplement at least 3 months prior to conception versus the benefits of commencing the same supplement at 12 weeks of gestational age. |
| Jul. 2013-<br>Dec. 2013 | Study Coordinator. ACTwatch: The DRC Outlet Survey 2013, Kinshasa and Katanga Provinces, DRC.<br>The aim of the study was to provide evidence to support national and global policy and funding decisions to improve malaria case management through provision of timely, relevant and quality information on the antimalarial market. |
| June 2011-<br>June 2013 | Supervisor. Evaluation of mass distribution campaigns of LLIN in the Provinces of Kinshasa, Bas-Congo, Orientale, Kasai-Oriental, Kasai-Occidental and Bandundu, DRC.<br>The aim if these surveys was to assess LLIN ownership and usage before and after the mass distribution campaigns. |
| Aug 2010-<br>Apr. 2011 | Clinician in a rural General Hospital of Reference, Province of Sankuru, DRC. |

**Oral presentations and posters**

| | |
|---|---|
| Sep. 2022 | "Rectal Artesunate for the management of severe malaria in the Democratic Republic of the Congo". Oral presentation for the 7th Speed talks on malaria, Basel, Switzerland. |
| Mar. 2022 | "Danger signs and management of suspected severe malaria cases at community level and in referral health facilities: an operational study in the Democratic Republic of the Congo". Oral presentation for the Monday seminar: Advances in Infection Biology, Epidemiology and Global Public Health, Basel, Switzerland. |
| May 2021 | "Factors associated with mortality in children under 5 years of age with severe malaria in the Democratic Republic of the Congo". Oral presentation for the 4th Malaria Scientific Days, Kinshasa, DRC. |

May 2021 "Costs of implementing pre-referral Rectal Artesunate and healthcare provision in the Democratic Republic of Congo" Poster presentation for the 4th Malaria Scientific Days, Kinshasa, DRC.

Nov. 2020 "The quality of case management for severe malaria episodes and its impact on the health outcomes in remote endemic settings of the Democratic Republic of the Congo". Poster presentation for the American Society of Tropical Medicine and Hygiene 69th Annual Meeting, virtual.

## Publications

### Unpublished (under review papers)

**Okitawutshu J**, Tshefu A.K, Kalenga JC, Delvento G, Burri C, W. Hetzel M.W., Lengeler C., Aita Signorell. "Assessing caregivers' perceptions of treatment seeking for suspected severe malaria in the Democratic Republic of the Congo" (2022).

### Published articles

Signorell, A., Awor, P., **Okitawutshu, J.**, Tshefu, A., Omoluabi, E., Hetzel, M. W., Athieno, P., Kimera, J., Tumukunde, G., Angiro, I., Kalenga, J. C., Akano, B. K., Ayodeji, K., Okon, C., Yusuf, O., Delvento, G., Lee, T. T., Brunner, N. C., Lambiris, M. J., Okuma, J., … Burri, C. (2023). Health worker compliance with severe malaria treatment guidelines in the context of implementing pre-referral rectal artesunate in the Democratic Republic of the Congo, Nigeria, and Uganda: An operational study. *PLoS medicine*, ***20***(2), e1004189.

Hetzel, M. W., **J. Okitawutshu**, A. Tshefu, E. Omoluabi, P. Awor, A. Signorell, N. C. Brunner, et al. (2022). "Effectiveness of rectal artesunate as pre-referral treatment for severe malaria in children under 5 years of age: a multi-country observational study." *BMC Med* **20**(1): 343.

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