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# Management of suspected severe malaria during stepped-wedge roll-out of rectal artesunate and amoxicillin: care-seeking and treatment pathways in Kapolowe, Democratic Republic of the Congo

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## Abstract

# Background

Rectal artesunate (RAS) delivered through integrated community case management aims to shorten the delay to definitive treatment of severe malaria. Evidence on how adding RAS and amoxicillin to community health worker (CHW) kits affects care-seeking and treatment pathways is limited, particularly in the Democratic Republic of the Congo (DRC).

# Methods

Nested in the SEMA ReACT hybrid study, the national malaria programme rolled out RAS and amoxicillin through CHW kits in a stepped-wedge design in Kapolowe Health District, DRC. In four sentinel health areas, we enrolled 1356 children aged 6–59 months with suspected severe malaria and 1175 with uncomplicated malaria (March 2024–January 2026), with Day 14 follow-up. The exposure was health-area availability of RAS and amoxicillin (none, RAS only, RAS plus amoxicillin). The primary outcome was formal care-seeking within 24 hours of symptom onset; secondary outcomes covered informal care, management, referral completion and adherence to ACT treatment. We used logistic regression adjusted for phase, site, season, distance and child characteristics.

# Results

Timely formal care-seeking was uncommon (5%, 8% and 7%) and not associated with RAS (adjusted odds ratio 0.80, 95% CI 0.23–2.84) or RAS-plus-amoxicillin availability (0.40, 0.06–2.73). Informal treatment before formal contact remained common (70–76%); informal antimalarial use fell from 12% to 4% ($p = 0.007$), and use of antipyretics alone rose from 55% to 68% ($p = 0.04$). Informal care after formal contact declined from 25% to 13% ($p < 0.001$). Referral-facility attendance rose from 1% to 6% ($p < 0.001$). Off-guideline community treatment fell from 92% to 0%, and 82–92% of children given RAS subsequently received artemisinin-based combination therapy (ACT). At hospital, injectable artesunate plus ACT rose from 65% to 95% ($p < 0.001$). Among children interviewed on Day 14, ACT-course completion was 84%, 91% and 99%.

# Conclusions

Periods with RAS and amoxicillin in CHW kits were associated with more guideline-consistent treatment after first contact, including follow-on ACT for most children who did not complete referral, but not with timely care-seeking. Referral completion remained low but did not decline after RAS introduction. With four sentinel clusters and provider-documented treatment, these associations should be interpreted cautiously.

# Trial registration:

ClinicalTrials.gov, NCT06806956. Registered 29 November 2024.

## Background

Malaria caused an estimated 282 million cases and 610 000 deaths worldwide in 2024. The World Health Organization (WHO) African Region accounted for about 95% of global malaria deaths, and children under five years accounted for approximately 75% of malaria deaths in the region [1]. The Democratic Republic of the Congo (DRC) ranked second in malaria mortality, with an estimated 11–12% of malaria deaths in the region [1]. For children with severe malaria, the risk of death increases rapidly with each hour of delay before effective antimalarial treatment [2], and survival depends on prompt access to parenteral artesunate followed by a complete course of artemisinin-based combination therapy (ACT) [3]. However, in many rural African settings, including large parts of the DRC, long travel distances, financial barriers and poor availability of essential commodities at health facilities and in communities continue to delay or prevent access to definitive treatment [2]. At the same time, the pathways that families follow when a child develops a severe febrile illness are complex and pluralistic [4, 5].

WHO recommends rectal artesunate (RAS) as pre-referral treatment for children with suspected severe malaria who cannot rapidly access full parenteral treatment [3]. RAS should be administered as soon as danger signs are identified and followed by prompt referral for definitive parenteral antimalarial treatment. In parallel, WHO and UNICEF have promoted integrated community case management (iCCM) as a core strategy to expand access to treatment for malaria, pneumonia and diarrhoea among underserved children through trained community health workers (CHWs) [6]. Within this platform, adding RAS and amoxicillin to existing CHW drug kits enables CHWs to manage a broader spectrum of childhood febrile illness close to home and could influence how and where caregivers seek care for acutely ill children.

In this analysis, we used the phased roll-out of RAS and amoxicillin through CHWs to examine how care-seeking and treatment pathways for children with suspected severe malaria changed over time in Kapolowe Health District. Specifically, we assessed (i) timely formal care-seeking, defined as seeking care from the formal health system within 24 hours of symptom onset; (ii) use of informal care and associated treatments before and after first formal contact; (iii) management and treatment received at community and hospital level after first contact, including referral completion; and (iv) adherence to antimalarial and antibiotic treatment at Day 14. We hypothesised that deployment of RAS and amoxicillin within CHW iCCM kits would increase timely access to formal care, reduce reliance on informal providers, and improve the completeness and appropriateness of treatment received across the care pathway.

## Methods

# Study design and setting

This analysis is nested within the Severe Malaria Treatment with Rectal Artesunate and Artemisinin-Based Combination Therapy in Remote Settings (SEMA ReACT) study, an effectiveness–implementation hybrid type 3 trial conducted in Zambia and the DRC, registered at ClinicalTrials.gov (NCT06806956) and described in detail elsewhere [7].

The present analysis focuses on Kapolowe Health District, Haut-Katanga Province, south-eastern DRC. For the management of suspected severe malaria, health posts operate in practice as an extension of the CHW/iCCM level: both health posts and CHWs are expected to recognise danger signs and refer all suspected severe cases to hospital for definitive parenteral treatment, without providing parenteral therapy themselves [8].

The Ministry of Public Health, through the National Malaria Control Programme (Programme National de Lutte contre le Paludisme, PNLP), implemented reinforced iCCM in Kapolowe using a stepped-wedge design in which the 16 health areas of the district were randomly allocated to an early or a late implementation sequence (eight each). The randomisation procedure and sample size are described in the protocol [7]. The intervention was introduced in four sequential phases (Fig. 1):

1. Phase 1 (11 March – 30 June 2024; baseline): all health areas provided routine iCCM only, and CHWs were expected to refer all suspected severe cases.
2. Phase 2 (1 July 2024–31 January 2025): RAS was added to CHW kits in the early group of health areas, while the late group continued routine iCCM without RAS or amoxicillin.
3. Phase 3 (1 February – 14 September 2025): RAS was extended to all health areas, and amoxicillin was added to CHW kits in the early group only.
4. Phase 4 (15 September 2025–20 January 2026): both RAS and amoxicillin were available in CHW kits in all health areas.

Because Phase 4 began in mid-September, almost all of it fell in the rainy season (October–April), whereas Phases 1–3 each spanned both seasons. All health areas eventually received the full intervention.

After each implementation phase, a two-day feedback and evaluation meeting was held in Kapolowe. These meetings brought together representatives of the Ministry of Public Health and the PNLP, district managers responsible for drug supply, health-facility staff and CHWs. Participants reviewed emerging data, discussed practical challenges and agreed actions to strengthen commodity availability, health-system readiness and the tracing of enrolled children for follow-up before the next phase.

# Participants and data collection

Two sentinel health areas were selected from each of the early and late implementation groups (four sentinel health areas in total) for close patient follow-up, as specified in the parent protocol [7]. In these

sentinel areas, CHWs and staff at health posts or primary facilities identified and enrolled eligible children during routine iCCM consultations; children presenting directly to the referral hospital serving each sentinel area were enrolled there. Eligible participants were children aged 6–59 months presenting with suspected severe malaria or uncomplicated malaria according to iCCM case definitions. Suspected severe malaria was defined by at least one iCCM danger sign together with a positive malaria rapid diagnostic test (mRDT); uncomplicated malaria was defined by a positive mRDT and no danger signs. During mRDT stock-outs, children with iCCM danger signs were managed as suspected severe malaria in line with iCCM guidance and were enrolled as such (33 children; Fig. 2).

Children with uncomplicated malaria were enrolled as a concurrent comparison group to distinguish changes specific to the severe-malaria pathway from general changes in the local treatment environment over the same period. For each child enrolled with suspected severe malaria, CHWs and health-facility staff were asked to enrol the next eligible child with uncomplicated malaria.

After written informed consent from the parent or guardian, CHWs or health-facility workers completed a Day 0 case report form (CRF) adapted from the iCCM register. It captured demographic information, access-to-care variables (time and distance from home, prior treatment-seeking and use of informal providers), clinical signs and symptoms, danger signs, mRDT results, iCCM diagnosis, treatments given at the first point of contact and whether the child was referred to a higher-level facility. For children referred to hospital who completed referral, a treatment follow-up form documented all treatments received at the referral facility. Day 0 activities were completed as part of routine care, without the SEMA ReACT research team present.

SEMA ReACT research assistants conducted active follow-up visits on Day 14 for all enrolled children. The Day 14 CRF recorded the child's vital status, treatment-seeking since the Day 0 visit (formal and informal providers consulted, in chronological order), adherence to treatments prescribed at Day 0 and reasons for non-completion of referral. A Day 28 visit was planned in the parent protocol, but the present analysis is restricted to Day 0 and Day 14 information.

## Exposure and outcomes

The main exposure was health-area availability of RAS and amoxicillin, coded at child level as a three-category treatment package according to the implementation phase at enrolment and the implementation group of the recruiting health area: (i) no RAS or amoxicillin available (routine iCCM only); (ii) RAS available only; and (iii) RAS plus amoxicillin available. Children recruited at hospital were assigned the exposure of the health area served by the recruiting facility. Exposure followed the programmatic phase dates; short within-phase stock-outs were not taken into account.

The primary outcome was timely formal care-seeking, defined as the caregiver seeking care from the formal health system (CHW, health post or health facility) within 24 hours of symptom onset. It was operationalised as a caregiver-reported illness duration of 0 or 1 day at first formal contact.

Secondary outcomes concerned informal care. Informal care before formal contact indicated whether the caregiver sought any informal care (self-medication from home stocks, drug shops or pharmacies, traditional healers, churches or other sources) before the child's first contact with the formal system. Among children who used informal care before formal contact, we assessed receipt of (i) any antimalarial, (ii) any antibiotic and (iii) antipyretics or analgesics alone, that is, without an antimalarial or antibiotic. Medicines were classified from free-text entries into antipyretic/analgesic, antibiotic, antimalarial and traditional/herbal categories (Additional file 1: Table S2). Informal care after formal contact indicated whether the caregiver sought any informal care between the first formal visit and Day 14, either in parallel with or instead of additional formal care.

Further outcomes described management after first formal contact. At community level, RAS followed by ACT, with or without amoxicillin, was considered the intended treatment package; ACT could be given by the CHW or health post, at the referral facility or, when referral was not completed, obtained afterwards from an informal provider, and the last source is reported separately. Off-guideline care at community level was defined as treatment given in place of referral in the absence of RAS, typically oral ACT with or without symptomatic or supportive medicines. At hospital level, injectable artesunate followed by ACT was considered recommended treatment [3]; injectable quinine followed by ACT is reported separately. Adherence to ACT or amoxicillin was defined as the caregiver's report at Day 14 of having given all doses as prescribed on the Day 0 CRF and was assessed among children interviewed at Day 14. Independently of the referral advice documented on the Day 0 CRF, the Day 14 CRF also recorded whether the caregiver reported having received advice to go to hospital and, when referral was not completed, the caregiver's stated reason. Children whose caregiver could not be located or interviewed at Day 14 were classified as lost to follow-up.

# Statistical analysis

Baseline characteristics were summarised by treatment package using proportions with 95% confidence intervals (CIs) for categorical variables and medians with interquartile ranges for continuous variables. Care-seeking patterns, management after first contact and Day 14 outcomes were summarised as proportions by treatment package. Each intervention period was compared with the period without RAS or amoxicillin, and the two intervention periods with each other, using Fisher's exact test. Two-sided p-values were Bonferroni-adjusted within each table section and malaria severity stratum (24 tests per stratum for care-seeking; 17 and 21 tests for community- and hospital-level management of severe malaria; 12 and 9 tests for Day 14 outcomes in severe and uncomplicated malaria), and adjusted values above 0.99 are reported as > 0.99. These descriptive tests treat children as independent observations and do not account for clustering within health areas; site-level intraclass correlations are reported in Additional file 1: Table S8.

For the primary outcome, children with severe and uncomplicated malaria were analysed separately, as pre-specified. For children with severe malaria, we fitted a penalised (Firth) logistic regression model, chosen because the outcome was rare, with timely formal care-seeking as the dependent variable and

the three-level treatment package as the main exposure. Given only four clusters, site was included as a fixed effect rather than a random effect [9, 10]. The model adjusted for implementation phase, season, distance to the nearest facility (≤ 5 km or > 5 km), child sex and age, previous malaria treatment, mode of transport (on foot or bicycle/public transport), source of recruitment, informal care before formal contact and number of iCCM danger signs.

For secondary care-seeking outcomes, children with severe and uncomplicated malaria were combined. Logistic regression was used for informal care before formal contact and, among children who used informal care before formal contact, for receipt of antimalarials, antibiotics and antipyretics alone. These models used the same exposure, site fixed effects and covariates as the primary model, except that malaria severity (severe or uncomplicated) replaced the number of danger signs and informal care before formal contact was not included. Results are presented as odds ratios with 95% CIs.

Because RAS and amoxicillin were introduced in a stepped-wedge roll-out, implementation phase (1–4) was included as a categorical time variable. Because treatment package and phase are related by design, we assessed collinearity with generalised variance inflation factors (Additional file 1: Table S9). Collinearity was moderate, and both treatment package and phase were retained in the final models.

All analyses were performed in R version 4.6.1, using the logistf package for penalised logistic regression, lme4 for random-intercept models and car for variance inflation factors. Large language model tools were used to assist with language editing and consistency checking of the manuscript; the authors reviewed all content and take full responsibility for it.

## Results

# Participants and characteristics by exposure period

Between March 2024 and January 2026, 2531 children were enrolled in the four sentinel health areas: 1356 with suspected severe malaria, including 33 managed as severe malaria without an mRDT during stock-outs, and 1175 with uncomplicated malaria (Fig. 2). Of the children with suspected severe malaria, 600 (44%) were enrolled during periods without community-level RAS or amoxicillin, 398 (29%) when RAS was available and 358 (26%) when RAS plus amoxicillin was available (Table 1). Median age was 19.5 months (IQR 11–33), 22 months (12–32) and 24 months (14–36), respectively; 51%, 50% and 57% were male. Previous malaria treatment and multiple iCCM danger signs were similarly common across exposure periods. Most children were recruited at health posts (80%, 72% and 71%, respectively).

Table 1
Characteristics of children with suspected severe malaria by community-level availability of rectal artesunate and amoxicillin

| Characteristic | Category | No RAS/Amox, N = 600 | RAS, N = 398 | RAS + Amox, N = 358 |
|---|---|---|---|---|
| | | % (95% CI) | % (95% CI) | % (95% CI) |
| Age, months, median [IQR] | | 19.5 [11–33] | 22 [12–32] | 24 [14–36] |
| Sex[a] | Male | 51 (47–55) | 50 (45–55) | 57 (52–62) |
| | Female | 49 (45–53) | 50 (45–55) | 42 (37–48) |
| Previous malaria treatment | No | 67 (63–70) | 71 (66–75) | 69 (64–73) |
| | Yes | 33 (29–37) | 29 (25–34) | 31 (27–36) |
| Transport | On foot | 52 (48–55) | 49 (45–54) | 47 (42–52) |
| | Public transport | 46 (42–50) | 49 (44–54) | 51 (46–57) |
| | Bicycle | 3 (2–4) | 1 (1–3) | 2 (1–4) |
| Distance to nearest facility | 0–5 km | 73 (69–76) | 67 (63–72) | 48 (43–53) |
| | > 5 km | 27 (24–31) | 33 (28–37) | 52 (47–57) |
| Season | Rainy | 60 (57–64) | 51 (46–56) | 82 (77–85) |
| | Dry | 40 (36–43) | 49 (44–54) | 18 (15–23) |
| Source of recruitment | Health post | 80 (77–83) | 72 (68–76) | 71 (66–76) |
| | CHW | 12 (10–15) | 13 (10–16) | 13 (10–17) |
| | Hospital | 8 (6–10) | 15 (12–19) | 16 (12–20) |

Values are percentages (95% CI) unless stated otherwise. RAS: rectal artesunate; Amox: amoxicillin; CHW: community health worker; iCCM: integrated community case management; IQR: interquartile range. [a]Sex was missing for two children.

| Characteristic | Category | No RAS/Amox, N = 600 | RAS, N = 398 | RAS + Amox, N = 358 |
|---|---|---|---|---|
| | | % (95% CI) | % (95% CI) | % (95% CI) |
| Implementation phase | Phase 1 | 56 (52–60) | – | – |
| | Phase 2 | 44 (40–48) | 49 (44–54) | – |
| | Phase 3 | – | 51 (46–56) | 32 (27–37) |
| | Phase 4 | – | – | 68 (63–73) |
| Site | Kapo | 26 (22–29) | 25 (21–29) | 27 (23–32) |
| | Kyembe 2 | 26 (23–30) | 27 (23–32) | 36 (32–41) |
| | Koni 1 | 39 (35–43) | 23 (19–27) | 15 (12–19) |
| | Koni 2 | 9 (7–11) | 25 (21–30) | 22 (18–26) |
| iCCM danger signs | One | 23 (20–27) | 26 (22–31) | 25 (21–30) |
| | Multiple | 77 (73–80) | 74 (69–78) | 75 (70–79) |

Values are percentages (95% CI) unless stated otherwise. RAS: rectal artesunate; Amox: amoxicillin; CHW: community health worker; iCCM: integrated community case management; IQR: interquartile range. [a]Sex was missing for two children.

Children enrolled during RAS-plus-amoxicillin availability were more often recruited during the rainy season (82% vs 60% without RAS or amoxicillin and 51% with RAS), reflecting the timing of Phase 4, and more often lived more than 5 km from the nearest facility (52% vs 27% and 33%, respectively). The exposure periods therefore differed in two determinants of care-seeking, and the adjusted estimates below depend on adequate adjustment for season and distance. Characteristics of children with uncomplicated malaria are shown in Additional file 1: Table S1.

## Care-seeking before and after first formal contact

Timely formal care-seeking within 24 hours was uncommon among children with suspected severe malaria: 27/600 (5%) without RAS or amoxicillin, 30/398 (8%; p > 0.99) with RAS and 25/358 (7%; p > 0.99) with RAS plus amoxicillin (Table 2). In unadjusted analysis, RAS availability was associated with higher odds of timely care-seeking (crude odds ratio 1.73; 95% CI 1.01–2.97), but after adjustment

neither RAS availability (aOR 0.80; 95% CI 0.23–2.84; p = 0.72) nor RAS-plus-amoxicillin availability (aOR 0.40; 95% CI 0.06–2.73; p = 0.35) was associated with timely formal care-seeking (Table 3; Additional file 1: Table S3). Among children with uncomplicated malaria, timely formal care-seeking was 8%, 4% (p = 0.60) and 8% (p > 0.99), respectively (Table 2).

Table 2
Care-seeking before and after first formal contact by community-level availability of rectal artesunate and amoxicillin

| | No RAS/Amox | RAS | p[a] | RAS + Amox | p[a] |
|---|---|---|---|---|---|
| **Suspected severe malaria (N = 600 / 398 / 358)** | | | | | |
| **Before first formal contact** | | | | | |
| Formal care within 24 h of symptom onset[b] | 27/600 (5) | 30/398 (8) | > 0.99 | 25/358 (7) | > 0.99 |
| Informal treatment before formal care | 422/600 (70) | 288/398 (72) | > 0.99 | 272/358 (76) | > 0.99 |
| Antimalarial[c] | 50/422 (12) | 19/288 (7) | 0.49 | 11/272 (4) | 0.007 |
| Antibiotic[c] | 106/422 (25) | 78/288 (27) | > 0.99 | 69/272 (25) | > 0.99 |
| Antipyretic/analgesic only[c,d] | 234/422 (55) | 174/288 (60) | > 0.99 | 184/272 (68) | 0.04 |
| Traditional medicine[c] | 22/422 (5) | 6/288 (2) | > 0.99 | 3/272 (1) | 0.13 |
| Over-the-counter drug shop[c] | 363/422 (86) | 261/288 (91) | > 0.99 | 237/272 (87) | > 0.99 |
| Self-treatment[c] | 45/422 (11) | 17/288 (6) | 0.72 | 25/272 (9) | > 0.99 |
| Traditional healer[c] | 47/422 (11) | 16/288 (6) | 0.25 | 4/272 (1) | < 0.001 |
| Other source[c] | 28/422 (7) | 6/288 (2) | 0.15 | 8/272 (3) | 0.85 |
| **Between Day 0 and Day 14[e]** | | | | | |
| Additional formal care | 3/525 (0.6) | 5/397 (1.3) | > 0.99 | 3/356 (0.8) | > 0.99 |
| Informal care | 133/525 (25) | 81/397 (20) | > 0.99 | 46/356 (13) | < 0.001 |
| **Uncomplicated malaria (N = 558 / 350 / 267)** | | | | | |
| **Before first formal contact** | | | | | |

Values are n/N (%). RAS: rectal artesunate; Amox: amoxicillin. [a]Fisher's exact test versus No RAS/Amox, Bonferroni-adjusted for 24 tests within each severity stratum. [b]Caregiver-reported illness duration of 0 or 1 day at first formal contact. [c]Among children who received informal treatment before formal care; categories are not mutually exclusive. [d]Antipyretic or analgesic without an antimalarial or antibiotic. [e]Among children interviewed at Day 14 who answered the question on additional care.

| | No RAS/Amox | RAS | p[a] | RAS + Amox | p[a] |
|---|---|---|---|---|---|
| **Suspected severe malaria (N = 600 / 398 / 358)** | | | | | |
| **Before first formal contact** | | | | | |
| Formal care within 24 h of symptom onset[b] | 44/558 (8) | 14/350 (4) | 0.60 | 22/267 (8) | > 0.99 |
| Informal treatment before formal care | 351/558 (63) | 238/350 (68) | > 0.99 | 189/267 (71) | 0.68 |
| Antimalarial[c] | 42/351 (12) | 6/238 (3) | < 0.001 | 7/189 (4) | 0.03 |
| Antibiotic[c] | 91/351 (26) | 73/238 (31) | > 0.99 | 51/189 (27) | > 0.99 |
| Antipyretic/analgesic only[c,d] | 212/351 (60) | 153/238 (64) | > 0.99 | 126/189 (67) | > 0.99 |
| Traditional medicine[c] | 2/351 (1) | 0/238 (0) | > 0.99 | 2/189 (1) | > 0.99 |
| Over-the-counter drug shop[c] | 309/351 (88) | 220/238 (92) | > 0.99 | 168/189 (89) | > 0.99 |
| Self-treatment[c] | 34/351 (10) | 14/238 (6) | > 0.99 | 18/189 (10) | > 0.99 |
| Traditional healer[c] | 21/351 (6) | 3/238 (1) | 0.11 | 2/189 (1) | 0.15 |
| Other source[c] | 17/351 (5) | 2/238 (1) | 0.18 | 3/189 (2) | > 0.99 |
| **Between Day 0 and Day 14[e]** | | | | | |
| Additional formal care | 3/496 (0.6) | 2/347 (0.6) | > 0.99 | 0/267 (0) | > 0.99 |
| Informal care | 95/496 (19) | 52/347 (15) | > 0.99 | 24/267 (9) | 0.004 |

Values are n/N (%). RAS: rectal artesunate; Amox: amoxicillin. [a]Fisher's exact test versus No RAS/Amox, Bonferroni-adjusted for 24 tests within each severity stratum. [b]Caregiver-reported illness duration of 0 or 1 day at first formal contact. [c]Among children who received informal treatment before formal care; categories are not mutually exclusive. [d]Antipyretic or analgesic without an antimalarial or antibiotic. [e]Among children interviewed at Day 14 who answered the question on additional care.

Table 3
Adjusted associations between community-level availability of rectal artesunate and amoxicillin and care-seeking outcomes

| Outcome | No RAS/Amox n/N | RAS n/N | RAS aOR (95% CI) | p | RAS + Amox n/N | RAS + Amox aOR (95% CI) | p |
|---|---|---|---|---|---|---|---|
| **Suspected severe malaria**[a] | | | | | | | |
| Formal care within 24 h of symptom onset | 27/600 | 30/398 | 0.80 (0.23–2.84) | 0.72 | 25/358 | 0.40 (0.06–2.73) | 0.35 |
| **Severe and uncomplicated malaria combined**[b] | | | | | | | |
| Informal treatment before formal care | 773/1158 | 526/748 | 1.38 (0.91–2.11) | 0.13 | 461/625 | 2.43 (1.15–5.13) | 0.02 |
| Antimalarial[c] | 92/773 | 25/526 | 0.22 (0.08–0.57) | 0.003 | 18/461 | 0.13 (0.02–0.65) | 0.02 |
| Antibiotic[c] | 197/773 | 151/526 | 0.80 (0.47–1.36) | 0.41 | 120/461 | 0.40 (0.16–1.02) | 0.06 |
| Antipyretic/analgesic only[c] | 446/773 | 327/526 | 1.60 (0.99–2.58) | 0.06 | 310/461 | 3.62 (1.59–8.29) | < 0.01 |

aOR: adjusted odds ratio, with No RAS/Amox as reference; RAS: rectal artesunate; Amox: amoxicillin. [a]Firth penalised logistic regression adjusted for implementation phase, site, season, distance, sex, age, previous malaria treatment, transport, source of recruitment, informal care before formal contact and number of danger signs. [b]Logistic regression adjusted for implementation phase, site, season, distance, sex, age, previous malaria treatment, transport, source of recruitment and malaria severity. [c]Among children who received informal treatment before formal care. Full models are shown in Additional file 1: Tables S3–S7.

Before first formal contact, informal treatment was common in both groups. It was reported by caregivers of 70%, 72% ($p > 0.99$) and 76% ($p > 0.99$) of children with suspected severe malaria, and of 63%, 68% ($p > 0.99$) and 71% ($p = 0.68$) of children with uncomplicated malaria, across the three periods. The medicines obtained changed over time. Among children with suspected severe malaria who received informal treatment, antimalarial use declined from 12% to 7% ($p = 0.49$) with RAS and 4% ($p = 0.007$) with RAS plus amoxicillin, whereas use of antipyretics alone increased from 55% to 60% ($p > 0.99$) and 68% ($p = 0.04$). Among children with uncomplicated malaria, antimalarial use declined from 12% to 3% ($p < 0.001$) and 4% ($p = 0.03$), and use of antipyretics alone rose from 60% to 64% and 67% (both $p > 0.99$).

In adjusted pooled models, RAS-plus-amoxicillin availability was associated with greater odds of informal treatment before formal contact (aOR 2.43; 95% CI 1.15–5.13; p = 0.02), consistent in direction with the unadjusted proportions (Table 3). Both intervention periods were associated with lower odds of pre-formal antimalarial use (RAS: aOR 0.22; 95% CI 0.08–0.57; p = 0.003; RAS plus amoxicillin: aOR 0.13; 95% CI 0.02–0.65; p = 0.02). Pre-formal antibiotic use showed a downward trend that did not reach statistical significance (RAS: aOR 0.80; 95% CI 0.47–1.36; p = 0.41; RAS plus amoxicillin: aOR 0.40; 95% CI 0.16–1.02; p = 0.06). Both intervention periods were associated with higher odds of using antipyretics alone, reaching significance for RAS plus amoxicillin (RAS: aOR 1.60; 95% CI 0.99–2.58; p = 0.06; RAS plus amoxicillin: aOR 3.62; 95% CI 1.59–8.29; p < 0.01).

The source of informal care also changed. Use of traditional healers declined among children with suspected severe malaria from 11% to 6% (p = 0.25) and 1% (p < 0.001), with a similar trend among children with uncomplicated malaria, from 6% to 1% in both intervention periods (p = 0.11 and p = 0.15). Over-the-counter drug shops remained the predominant source of informal care throughout (86–91% for suspected severe and 88–92% for uncomplicated malaria; p > 0.99 for all comparisons).

After first formal contact, informal care declined in both groups. Among children with suspected severe malaria interviewed at Day 14, it declined from 25% without RAS or amoxicillin to 20% with RAS (p > 0.99) and 13% with RAS plus amoxicillin (p < 0.001); the corresponding figures for uncomplicated malaria were 19%, 15% (p > 0.99) and 9% (p = 0.004). Additional formal care between Day 0 and Day 14 was rare (≤ 1.3%) in all periods.

## Management after first contact

Community-level management is described for the 553, 338 and 302 children with suspected severe malaria whose first formal contact was a CHW or health post; the remainder were enrolled directly at hospital (Table 4). Although referral was documented as advised for all of these children, referral-facility attendance remained low, increasing from 4/553 (1%) without RAS or amoxicillin to 13/338 (4%; p = 0.03) with RAS and 18/302 (6%; p < 0.001) with RAS plus amoxicillin.

Table 4
Community- and hospital-level management by community-level availability of rectal artesunate and amoxicillin

| | No RAS/Amox | RAS | p[a] | RAS + Amox | p[a] | p[b] |
|---|---|---|---|---|---|---|
| **Community level: suspected severe malaria[c] (N = 553 / 338 / 302)** | | | | | | |
| Received RAS | – | 335/338 (99) | – | 302/302 (100) | – | > 0.99 |
| Referral documented as advised | 553/553 (100) | 338/338 (100) | > 0.99 | 302/302 (100) | > 0.99 | > 0.99 |
| Attended referral facility | 4/553 (1) | 13/338 (4) | 0.03 | 18/302 (6) | < 0.001 | > 0.99 |
| **Among children who received RAS[d]** | | | | | | |
| RAS + amoxicillin + ACT[e] | – | – | – | 125/302 (41) | – | – |
| RAS + ACT[e] | – | 276/335 (82) | – | 154/302 (51) | – | < 0.001 |
| RAS followed by ACT, total[e] | – | 276/335 (82) | – | 279/302 (92) | – | 0.004 |
| RAS only | – | 46/335 (14) | – | 5/302 (2) | – | < 0.001 |
| **Without RAS** | | | | | | |
| ACT only | – | 2/338 (1) | – | 0/302 (0) | – | > 0.99 |
| Off-guideline care[f] | 508/553 (92) | 0/338 (0) | < 0.001 | 0/302 (0) | < 0.001 | > 0.99 |
| No treatment | 41/553 (7) | 1/338 (0.3) | < 0.001 | 0/302 (0) | < 0.001 | > 0.99 |
| **Community level: uncomplicated malaria (N = 522 / 292 / 239)** | | | | | | |

Values are n/N (%); – not applicable. RAS: rectal artesunate; Amox: amoxicillin; ACT: artemisinin-based combination therapy. [a]Fisher's exact test versus No RAS/Amox; [b]RAS versus RAS + Amox; Bonferroni-adjusted within each section (17 tests for community-level and 21 for hospital-level severe malaria; 3 for each uncomplicated section). [c]Children whose first formal contact was a CHW or health post. [d]Denominator: children who received RAS. [e]ACT given by the CHW or health post, at the referral facility or, when referral was not completed, obtained afterwards from an informal provider (23 children across both periods; Additional file 1: Figure S1). [f]Treatment given in place of referral in the absence of RAS, typically oral ACT with or without symptomatic or supportive medicines. [g]Children enrolled directly at hospital (47, 60 and 56) plus children who completed referral from community level (4, 13 and 18).

| | No RAS/Amox | RAS | p[a] | RAS + Amox | p[a] | p[b] |
|---|---|---|---|---|---|---|
| **Community level: suspected severe malaria[c] (N = 553 / 338 / 302)** | | | | | | |
| ACT | 493/522 (94) | 292/292 (100) | < 0.001 | 239/239 (100) | < 0.001 | > 0.99 |
| **Hospital level: suspected severe malaria[g] (N = 51 / 73 / 74)** | | | | | | |
| Injectable artesunate + ACT | 33/51 (65) | 60/73 (82) | 0.74 | 70/74 (95) | < 0.001 | 0.45 |
| Injectable artesunate only | 4/51 (8) | 4/73 (5) | > 0.99 | 3/74 (4) | > 0.99 | > 0.99 |
| Injectable quinine + ACT | 10/51 (20) | 7/73 (10) | > 0.99 | 1/74 (1) | 0.01 | 0.70 |
| Injectable quinine only | 0/51 (0) | 1/73 (1) | > 0.99 | 0/74 (0) | > 0.99 | > 0.99 |
| ACT only | 1/51 (2) | 1/73 (1) | > 0.99 | 0/74 (0) | > 0.99 | > 0.99 |
| No injectable and no ACT | 3/51 (6) | 0/73 (0) | > 0.99 | 0/74 (0) | > 0.99 | > 0.99 |
| Any injectable + ACT | 43/51 (84) | 67/73 (92) | > 0.99 | 71/74 (96) | > 0.99 | > 0.99 |
| **Hospital level: uncomplicated malaria (N = 36 / 58 / 28)** | | | | | | |
| ACT | 36/36 (100) | 58/58 (100) | > 0.99 | 28/28 (100) | > 0.99 | > 0.99 |

Values are n/N (%); – not applicable. RAS: rectal artesunate; Amox: amoxicillin; ACT: artemisinin-based combination therapy. [a]Fisher's exact test versus No RAS/Amox; [b]RAS versus RAS + Amox; Bonferroni-adjusted within each section (17 tests for community-level and 21 for hospital-level severe malaria; 3 for each uncomplicated section). [c]Children whose first formal contact was a CHW or health post. [d]Denominator: children who received RAS. [e]ACT given by the CHW or health post, at the referral facility or, when referral was not completed, obtained afterwards from an informal provider (23 children across both periods; Additional file 1: Figure S1). [f]Treatment given in place of referral in the absence of RAS, typically oral ACT with or without symptomatic or supportive medicines. [g]Children enrolled directly at hospital (47, 60 and 56) plus children who completed referral from community level (4, 13 and 18).

Without RAS or amoxicillin, off-guideline care in place of referral was documented for 508/553 children (92%) and no treatment for 41/553 (7%); both fell to zero or near zero once RAS became available (each $p < 0.001$). Oral ACT, often with symptomatic or supportive medicines, accounted for most off-guideline care.

During RAS availability, RAS was given to 335/338 children (99%). Despite referral-facility attendance of 4%, 276/335 children who received RAS (82%) subsequently received ACT. During RAS-plus-amoxicillin

availability, all 302 children received RAS; 154 (51%) subsequently received ACT and 125 (41%) amoxicillin plus ACT, together 279/302 (92%). Across both periods, 23 of the children who received RAS obtained their ACT from an informal provider after referral was not completed (Additional file 1: Figure S1). The proportion receiving RAS alone declined from 46/335 (14%) to 5/302 (2%; $p < 0.001$).

Among children with suspected severe malaria managed at hospital (those enrolled directly at hospital plus those who completed referral), injectable artesunate plus ACT was received by 33/51 (65%) without RAS or amoxicillin, 60/73 (82%; $p = 0.74$) with RAS and 70/74 (95%; $p < 0.001$) with RAS plus amoxicillin. Injectable quinine plus ACT declined from 10/51 (20%) to 7/73 (10%; $p > 0.99$) and 1/74 (1%; $p = 0.01$). Any injectable antimalarial followed by ACT was received by 84%, 92% and 96%, respectively ($p > 0.99$ for both comparisons).

Among children with uncomplicated malaria, ACT was given at first formal contact to 493/522 (94%) without RAS or amoxicillin and to all children during RAS (292/292) and RAS-plus-amoxicillin availability (239/239; both $p < 0.001$).

# Day 14 follow-up and treatment adherence

Without RAS or amoxicillin, 75/600 children with suspected severe malaria (12.5%) were lost to follow-up by Day 14, compared with none during RAS and RAS-plus-amoxicillin availability (Table 5). Loss to follow-up was concentrated in Phase 1: 73 of the 75 losses occurred in Phase 1 and two in Phase 2, when the late-group health areas were still without RAS. The same pattern was seen in uncomplicated malaria (60 of 62 losses in Phase 1). The decline in loss to follow-up coincided with tracing strategies agreed at the first phase-end feedback meeting and is therefore unlikely to reflect the treatment package itself.

Table 5
Day 14 follow-up and treatment completion by community-level availability of rectal artesunate and amoxicillin

| | No RAS/Amox | RAS | p[a] | RAS + Amox | p[a] | p[b] |
|---|---|---|---|---|---|---|
| **Suspected severe malaria (N = 600 / 398 / 358)** | | | | | | |
| Lost to follow-up[c] | 75/600 (12.5) | 0/398 (0) | < 0.001 | 0/358 (0) | < 0.001 | > 0.99 |
| Reported no referral advice[d] | 178/525 (33.9) | 85/398 (21.4) | < 0.001 | 61/358 (17.0) | < 0.001 | > 0.99 |
| Received ACT[e] | 499/600 (83.2) | 346/398 (86.9) | > 0.99 | 350/358 (97.8) | < 0.001 | < 0.001 |
| Completed ACT course[d] | 378/449 (84.2) | 316/346 (91.3) | 0.03 | 346/350 (98.9) | < 0.001 | < 0.001 |
| Received amoxicillin | – | – | – | 125/358 (34.9) | – | – |
| Completed amoxicillin course[d] | – | – | – | 122/125 (97.6) | – | – |
| **Uncomplicated malaria (N = 558 / 350 / 267)** | | | | | | |
| Lost to follow-up[c] | 61/558 (10.9) | 1/350 (0.3) | < 0.001 | 0/267 (0) | < 0.001 | > 0.99 |
| Received ACT[e] | 529/558 (94.8) | 350/350 (100) | < 0.001 | 267/267 (100) | < 0.001 | > 0.99 |
| Completed ACT course[d] | 471/473 (99.6) | 343/349 (98.3) | 0.70 | 267/267 (100) | > 0.99 | 0.35 |

Values are n/N (%); – not applicable. RAS: rectal artesunate; Amox: amoxicillin; ACT: artemisinin-based combination therapy. [a]Fisher's exact test versus No RAS/Amox; [b]RAS versus RAS + Amox; Bonferroni-adjusted for 12 (severe) and 9 (uncomplicated) tests. [c]73 of 75 (severe) and 60 of 62 (uncomplicated) losses occurred in Phase 1, before tracing strategies were introduced; the decline coincided with the introduction of these strategies and is unlikely to reflect the treatment package itself. [d]Among children interviewed at Day 14. [e]At any point between Day 0 and Day 14, from any source.

Among children interviewed at Day 14, the proportion of caregivers reporting that they had not received referral advice declined from 178/525 (33.9%) without RAS or amoxicillin to 85/398 (21.4%; p < 0.001) with RAS and 61/358 (17.0%; p < 0.001) with RAS plus amoxicillin.

Among children with suspected severe malaria who received ACT and were interviewed at Day 14, ACT-course completion was 378/449 (84.2%) without RAS or amoxicillin, 316/346 (91.3%; p = 0.03) with RAS and 346/350 (98.9%; p < 0.001) with RAS plus amoxicillin. Of 125 children given amoxicillin, 122 (97.6%)

completed the course. Among children with uncomplicated malaria, ACT was received by 529/558 (94.8%) without RAS or amoxicillin and by all children in both intervention periods; among those interviewed at Day 14, completion was high throughout: 471/473 (99.6%), 343/349 (98.3%; p = 0.70) and 267/267 (100%; p > 0.99). Adherence could not be assessed for children lost to follow-up.

# Discussion

In this pragmatic analysis nested in a stepped-wedge roll-out, availability of RAS, with or without amoxicillin, was not associated with improved timely formal care-seeking among children with suspected severe malaria. Informal treatment before the first formal contact remained common, although the medicines obtained changed: pre-formal antimalarial use declined while the use of antipyretics alone increased. By contrast, care after first formal contact changed substantially: informal care after formal contact declined, documented community treatment pathways became more consistent with the intended package, and recommended treatment at hospital increased. Referral-facility attendance remained low in all periods, as anticipated in this remote setting, but it did not decline after RAS introduction (1%, 4% and 6%), and most children who did not complete referral received follow-on ACT at community level. Taken together, the intervention periods were associated with more complete treatment after children entered the formal system, but not with the timing of entry into it.

Timely formal care-seeking remained uncommon throughout, and neither RAS nor RAS-plus-amoxicillin availability was associated with a significant improvement. This is consistent with evidence that delayed care-seeking for childhood malaria across sub-Saharan Africa (75–95% in some settings) is driven largely by factors that precede arrival at a facility, such as low socioeconomic status, informal home treatment, cultural norms, transport and caregiver confidence in community providers, rather than by commodity gaps alone [2, 11, 12]. Qualitative findings from the same Kapolowe population reinforce this pattern: mothers commonly delayed care and self-medicated, citing distance, impassable roads, lack of transport and the direct and indirect costs of care [5]. In access-framework terms, the intervention targeted the availability dimension of access, whereas affordability and acceptability were not directly addressed, a gap also described in other research on delays in childhood illness in the region [13]. This may explain the contrast with a programme in Malawi in which prompt care-seeking rose from 36% to 87% after mRDTs and pre-referral RAS were introduced alongside community meetings that informed caregivers in advance and addressed their questions and concerns [14]. Cultural and contextual differences may also have contributed.

Informal treatment was common among children with both suspected severe and uncomplicated malaria, reflecting an established regional pattern in which caregivers first seek medicines from drug shops, use treatments already at home or consult traditional healers before reaching the formal system [2, 5]. Nevertheless, the composition of pre-formal treatment changed: antimalarial use before formal care declined while the use of antipyretics alone increased, suggesting that caregivers continued to manage fever but relied less on informal sources for antimalarials. Because the antipyretic outcome was defined as antipyretics without an antimalarial or antibiotic, part of its increase is the counterpart of the

decline in antimalarial use. This shift matters for public health, because reliance on drug shops and vendors for antimalarials has been linked to incorrect dosing, poor adherence and the risk of resistance [15], and a comparable decline in first-resort informal care-seeking, from 12.9% to 1.9%, was reported after RAS introduction in Malawi [14]. One plausible explanation is improved ACT availability through health posts and other formal providers during implementation; this cannot be established from these data alone and should be examined alongside qualitative findings and commodity records. The lower level of informal care after first formal contact, observed in both suspected severe and uncomplicated malaria and strongest during RAS-plus-amoxicillin availability, is consistent with greater confidence in, or completeness of, care received after formal assessment. However, it reflects care-seeking behaviour, not clinical outcome; parasitological and PCR-corrected cure rates are being assessed separately.

Only 8% of children with suspected severe malaria were recruited directly at a hospital before RAS or amoxicillin was available, rising to 15% and 16% in the intervention periods, so reaching hospital-level care required completing a referral step for the large majority of children. Reaching hospital required a referral step for most children, and referral completion was low in all periods, consistent with the remote setting for which the SEMA ReACT model was designed. Concerns have been raised that RAS may falsely reassure caregivers and reduce referral completion [20]. We did not observe this: attendance at a referral facility did not fall after RAS became available and was higher in the intervention periods although this rise could also reflect the presence of the study. The pattern is consistent with other DRC studies, in which RAS availability and recruitment at primary health centres were associated with a greater likelihood of completing referral [16, 17], and differs from Uganda, where RAS availability was not associated with improved referral completion [18, 19]. The persistent gap appears to reflect structural barriers outside the direct control of the health ministry. Financial constraints were the leading reason for non-completion throughout, and distance became an increasingly cited barrier (Additional file 1: Figure S2), consistent with qualitative accounts from this population describing impassable roads, transport costs and financial hardship [5], and with the multi-country CARAMAL study, which found referral completion constrained by transport deficits and gaps in the broader continuum of care [20]. Near-universal reliance on out-of-pocket payment for transport and care in the DRC further limits what a community-level intervention can resolve alone [21].

CHW and facility CRFs recorded that referral was advised for essentially all children, yet at Day 14 a substantial minority of caregivers reported having received no such advice: 33.9% before RAS or amoxicillin was available, declining to 21.4% and 17.0% in the intervention periods. This divergence suggests that documented referral advice did not reliably translate into advice that caregivers understood or recalled, and that the improvement over time may reflect clearer or better-retained communication rather than a change in whether referral was nominally advised. This is consistent with qualitative evidence that caregiver understanding of referral instructions after RAS administration is often incomplete, even when providers report giving them [22]. The proportion of caregivers citing improvement of the child as their reason for not completing referral rose from 3% before RAS or amoxicillin availability to 49% with RAS and 63% with RAS plus amoxicillin. Following the CARAMAL study, it has been suggested that RAS may falsely reassure caregivers that their child has been

adequately treated, reducing the perceived urgency of referral [20]. In our setting, however, most children who did not complete referral received RAS followed by ACT at community level (82% and 92% in the two intervention periods), which makes genuine clinical improvement a plausible explanation. Confirming this will require the PCR-corrected cure-rate data.

The community-management findings show a substantial change in the documented treatment pathway. Before RAS or amoxicillin was available, with very few children reaching a referral facility, most received off-guideline care or no formal treatment. After implementation, RAS administration was nearly universal and most children subsequently received ACT. Both figures come from provider-completed records: the fall in documented off-guideline care from 92% to zero may partly reflect what workers were willing to record once a sanctioned alternative existed, rather than a complete change in practice.

The 8% of children who received RAS alone, pooled across both intervention periods, is nonetheless a concern. RAS given without a follow-on antimalarial or completed referral amounts to artemisinin monotherapy, which does not reliably clear parasitaemia and carries a recognised risk of recrudescence and selection of artemisinin-resistant parasites [23]. Some children obtained ACT from informal providers after receiving RAS, suggesting that some caregivers did not regard RAS as complete treatment and sought the next step when referral was not completed, plausibly because CHWs had explained during RAS administration that RAS is a temporary measure that must be followed by curative treatment [22]. However, ACT obtained outside the formal system may differ in dose, quality, counselling and documentation, carries its own risk of incorrect dosing or poor adherence [15], and cannot be considered equivalent to completion of the intended referral pathway. These children are the gap the SEMA ReACT model is designed to close: follow-on ACT at community level when referral is not completed, consistent with the WHO back-up plan [23]. The decline in RAS-only treatment from 14% to 2% suggests this was increasingly achieved. A scheduled CHW follow-up visit to every RAS-treated child, for example within 24 hours, could help close the remaining gap and confirm whether referral was completed. Such visits may also help to build trust in CHWs. Subsidized transport or other referral support to reduce access barriers remains a complementary measure [24].

Cases in which children with suspected severe malaria received ACT alone at community level could reflect the limited specificity of iCCM danger signs for true severe malaria, since a substantial proportion of children meeting clinical criteria for severe malaria have another underlying condition and may have uncomplicated malaria [25]. They could also reflect under-documentation: CHWs giving off-guideline treatment to a child they were meant to refer may be less likely to record this explicitly, because doing so falls outside their sanctioned scope of practice.

At hospital level, the high proportion of children who received injectable artesunate followed by ACT, together with the marked decline in injectable quinine, which is inferior for severe malaria [26, 27], is consistent with closer alignment with the recommended definitive treatment pathway. Possible contributing factors include local clinical practice, changing commodity availability and repeated discussion of severe-malaria management during the phase-end meetings. This structured, data-

informed feedback loop is consistent with evidence that reviewing stock and performance data with frontline and supply-chain staff improves health-worker practice and prevents commodity shortages [28–30]. Children recorded as receiving injectables without ACT, or ACT alone, at hospital could reflect documentation gaps or facility-level constraints, a problem also documented in CARAMAL, where directly observed treatment for severe malaria was frequently incomplete and completion with ACT was often left to the caregiver [20]; alternatively, ACT may have been prescribed but not dispensed or administered before discharge, which these data cannot distinguish.

Adherence to ACT and amoxicillin among children interviewed at Day 14 was high. This is in line with evidence that adherence to ACT, whether artesunate–amodiaquine or artemether–lumefantrine, is generally high in the DRC [31], that adherence is higher when the drug is dispensed directly rather than left to the caregiver to obtain with a prescription [24], and that adherence is higher when treatment is delivered through the public rather than the private sector [32]. These conditions applied throughout the community-level pathway, where RAS, ACT and amoxicillin were dispensed directly by CHWs as fixed public-sector courses.

This study has several strengths. It evaluated a real-world, Ministry-led roll-out rather than a researcher-delivered intervention, and it followed children across the care pathway from pre-formal treatment to formal assessment, referral, hospital management and Day 14 treatment completion. Including children with uncomplicated malaria as a comparison group was also informative: high ACT receipt and adherence in this group are consistent with changes in the wider local treatment environment over the study period, rather than only among children classified as having suspected severe malaria.

Several limitations should be considered. First, RAS and amoxicillin availability advanced with implementation phase, alongside calendar time, commodity distribution, programme learning and the structured feedback meetings. Collinearity between treatment package and phase was moderate rather than severe (Additional file 1: Table S9), allowing both to be included in the same models, but with four sentinel clusters some estimates were imprecise and secular trends or concurrent programme activities cannot be fully separated from the intervention. Second, timely care-seeking was uncommon (82 events among children with suspected severe malaria), so the pre-specified primary model was estimated with few events per parameter; Firth penalisation reduces small-sample bias, but the resulting confidence intervals are wide and a modest effect cannot be excluded. Third, the primary outcome relied on caregiver-reported illness duration recorded in whole days, so a duration of one day may include intervals somewhat longer than 24 hours. Caregivers also appeared to anchor their reports to different reference points, some describing the interval from fever onset and others from a specific danger sign; this became apparent only after a supplementary question on danger-sign timing was added from Phase 3 onward and may have introduced non-differential measurement error. Fourth, key variables, including referral advice and treatment given, relied on documentation by the CHW or facility worker and could not be independently verified, as illustrated by the discrepancy between documented and caregiver-reported referral advice. Documented off-guideline treatments, given by workers who are required to refer rather than treat suspected severe malaria when RAS is unavailable, could not have come from officially

supplied commodities for that purpose, and their accuracy and completeness cannot be confirmed. Fifth, loss to follow-up was concentrated in Phase 1; adherence and Day 14 outcomes were therefore assessed among children interviewed, but if children lost in Phase 1 differed from those followed up, baseline estimates may be biased. Sixth, pre-formal medicines were classified from free-text caregiver reports, which may have introduced misclassification. Seventh, the descriptive comparisons in Tables 2, 4 and 5 treat children as independent, although enrolment was clustered within four health areas, so the corresponding p-values are approximate. Finally, this paper addresses implementation and treatment pathways; clinical effectiveness outcomes, including mortality and PCR-corrected cure, require separate analysis.

# Conclusions

Reinforcing iCCM with RAS and amoxicillin, embedded within iterative feedback cycles, was associated with more guideline-consistent documented treatment pathways, including follow-on ACT for most children who could not complete referral, and with more use of injectable artesunate at hospital level. Referral completion remained low but did not decline after RAS introduction, and timely formal care-seeking did not differ between periods. Where referral is not feasible, community follow-on treatment with ACT offers a practical way to avoid leaving children on RAS alone, but it should be paired with strategies addressing transport, cost and communication barriers to referral.

# Abbreviations

ACT
Artemisinin-based combination therapy
aOR
Adjusted odds ratio
CHW
Community health worker
CI
Confidence interval
CRF
Case report form
DRC
Democratic Republic of the Congo
iCCM
Integrated community case management
IQR
Interquartile range
mRDT
Malaria rapid diagnostic test
PCR

Polymerase chain reaction
PNLP
Programme National de Lutte contre le Paludisme (National Malaria Control Programme)
RAS
Rectal artesunate
SEMA ReACT
Severe Malaria Treatment with Rectal Artesunate and Artemisinin-Based Combination Therapy in Remote Settings
WHO
World Health Organization

## Declarations

### Ethics approval and consent to participate

The study was approved by the National Health Ethics Committee (Comité National d'Éthique de la Santé) of the Democratic Republic of the Congo (reference 502/CNES/BN/PMMF/2023). Before enrolment, trained CHWs or health-facility staff read the consent form to the parent or legal guardian in Swahili, explaining the study objectives, procedures and duration, the voluntary nature of participation, the right to withdraw or decline questions at any time, the absence of financial compensation and the confidentiality of data, and providing contact details of the investigators and the ethics committee. Written informed consent was obtained from the parent or legal guardian of every participating child. All methods were performed in accordance with the Declaration of Helsinki.

### Consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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# Author Contribution

H.R., S.D., K.A., J.P.V.G., C.M. and H.M.M. conceived the study, acquired the funding and supervised the study. T.M., A.K., B.M., G.K., V.M.T., A.M.M., E.M.S., M.N., H.B. and G.M. contributed to the study design. T.M., J.S., D.B.K. and F.L.K. coordinated and implemented data collection in the field. B.M. and G.K. coordinated implementation of the roll-out with the National Malaria Control Programme. T.M. designed and managed the database, performed the statistical analysis and prepared the tables and figures. T.M. and D.B.K. wrote the main manuscript text. S.H., S.K., V.B. and G.L. contributed to interpretation of the findings and critically revised the manuscript for important intellectual content. All authors reviewed and approved the final manuscript and agree to be accountable for the work

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# Data Availability

The datasets generated and analysed during the current study are publicly are available from the corresponding author on reasonable request, subject to approval by the SEMA ReACT consortium and the National Health Ethics Committee of the Democratic Republic of the Congo.

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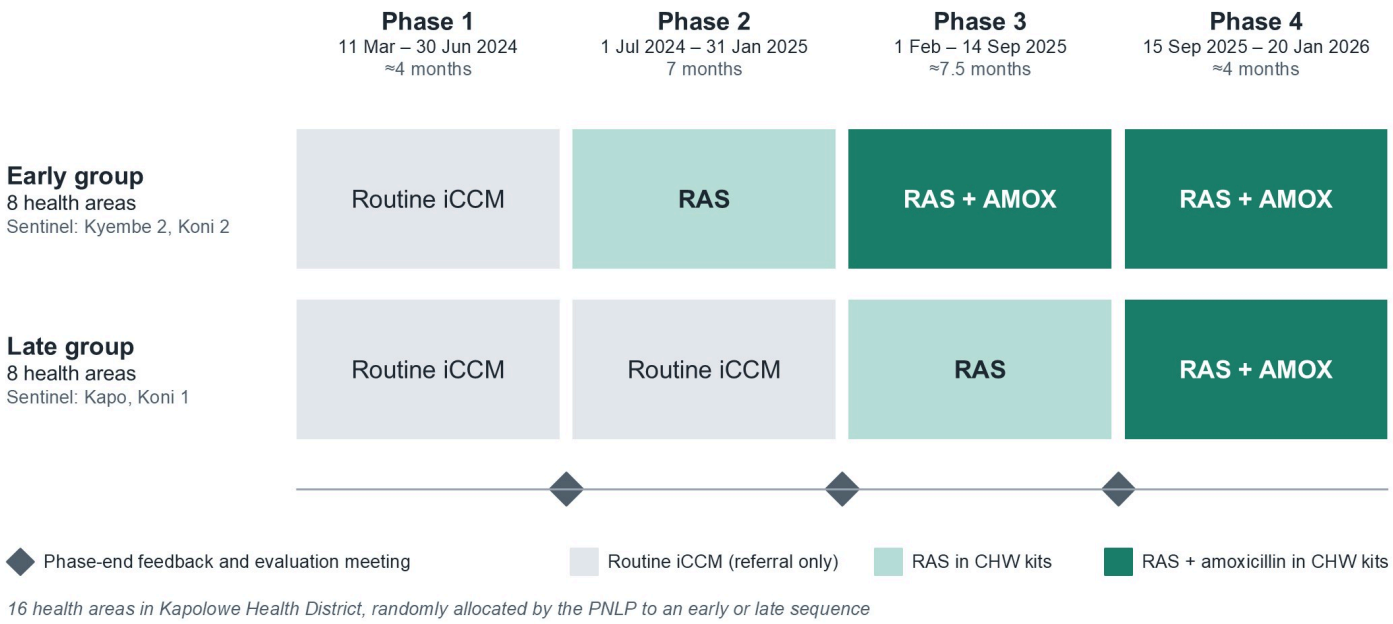
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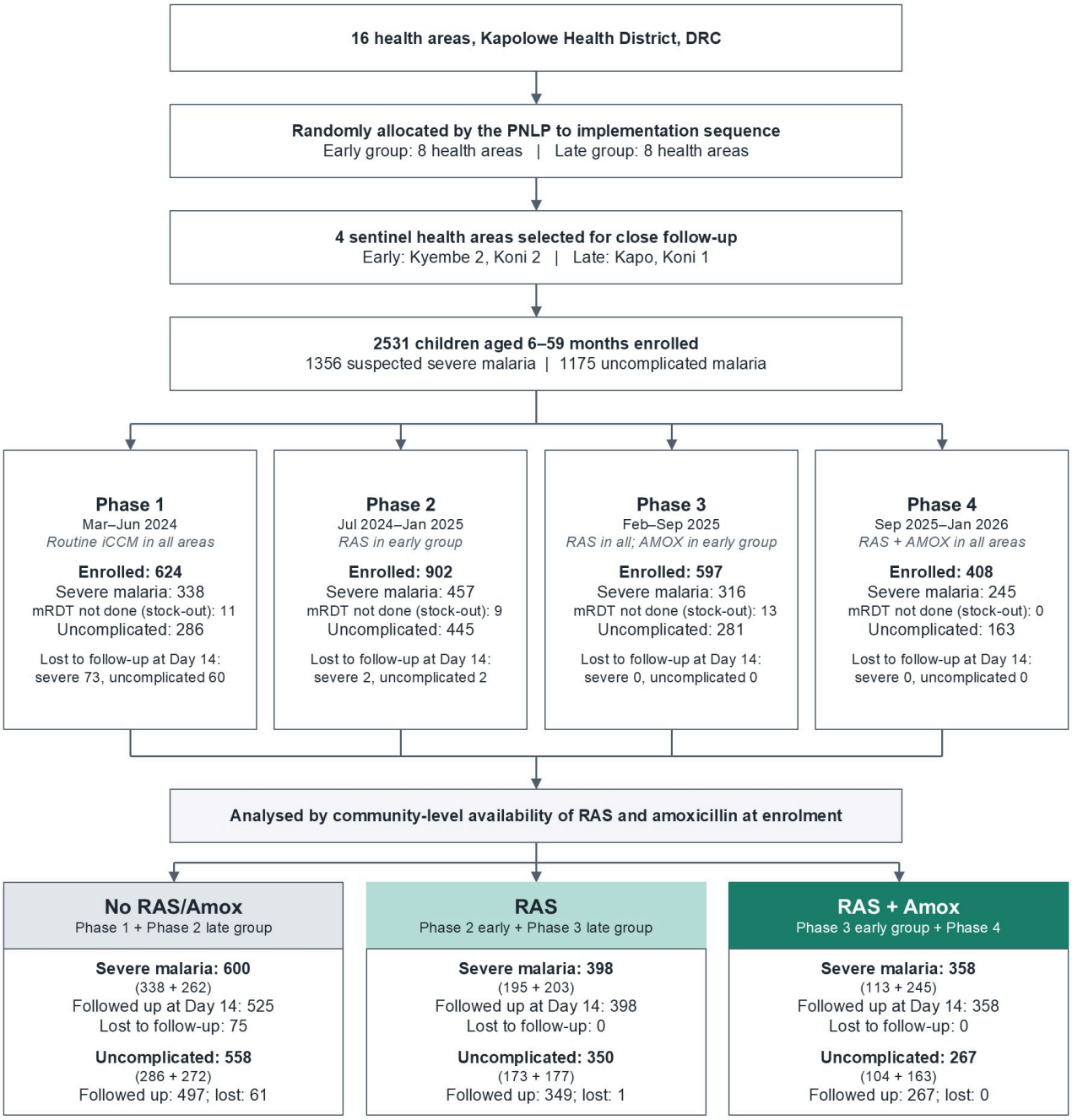
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# Figures




## Figure 1

**Stepped-wedge roll-out of reinforced iCCM with rectal artesunate and amoxicillin in Kapolowe Health District, Democratic Republic of the Congo.** The 16 health areas were randomly allocated by the National Malaria Control Programme to an early or late implementation sequence (eight each). RAS: rectal artesunate; AMOX: amoxicillin; iCCM: integrated community case management.




RAS: rectal artesunate; AMOX: amoxicillin; iCCM: integrated community case management; mRDT: malaria rapid diagnostic test; PNLP: National Malaria Control Programme. Children with danger signs and no mRDT because of stock-outs were managed and enrolled as suspected severe malaria. All children enrolled were included in the analysis.

## Figure 2

**Participant flow.** Children aged 6–59 months enrolled in the four sentinel health areas, by implementation phase and by community-level availability of rectal artesunate (RAS) and amoxicillin (AMOX). Children with iCCM danger signs for whom no malaria rapid diagnostic test (mRDT) could be performed because of stock-outs were managed and enrolled as suspected severe malaria.

# Supplementary Files

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