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Prereferral rectal artesunate and referral completion among children with suspected severe malaria in the Democratic Republic of the Congo, Nigeria and Uganda

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ABSTRACT

Introduction Children who receive prereferral rectal artesunate (RAS) require urgent referral to a health facility where appropriate treatment for severe malaria can be provided. However, the rapid improvement of a child's condition after RAS administration may influence a caregiver's decision to follow this recommendation. Currently, the evidence on the effect of RAS on referral completion is limited.

Methods An observational study accompanied the roll-out of RAS in three malaria endemic settings in the Democratic Republic of the Congo (DRC), Nigeria and Uganda. Community health workers and primary health centres enrolled children under 5 years with suspected severe malaria before and after the roll-out of RAS. All children were followed up 28 days after enrolment to assess their treatment-seeking pathways.

Results Referral completion was 67% (1408/2104) in DRC, 48% (287/600) in Nigeria and 58% (2170/3745) in Uganda. In DRC and Uganda, RAS users were less likely to complete referral than RAS non-users in the pre-roll-out phase (adjusted OR (aOR)=0.48, 95% CI 0.30 to 0.77 and aOR=0.72, 95% CI 0.58 to 0.88, respectively). Among children seeking care from a primary health centre in Nigeria, RAS users were less likely to complete referral compared with RAS non-users in the post-roll-out phase (aOR=0.18, 95% CI 0.05 to 0.71). In Uganda, among children who completed referral, RAS users were significantly more likely to complete referral on time than RAS non-users enrolled in the pre-roll-out phase (aOR=1.81, 95% CI 1.17 to 2.79).

Conclusions The findings of this study raise legitimate concerns that the roll-out of RAS may lead to lower referral completion in children who were administered prereferral RAS. To ensure that community-based programmes are effectively implemented, barriers to referral completion need to be addressed at all levels. Alternative effective treatment options should be provided to children unable to complete referral.

Trial registrstion number NCT03568344; ClinicalTrials.gov.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Prereferral rectal artesunate reduces case fatality in children with suspected severe malaria in the context of high referral completion.

⇒ Based on qualitative evidence, there are concerns that the administration of rectal artesunate may increase the risk of not completing referral.

WHAT THIS STUDY ADDS

⇒ There was a negative association between prereferral treatment with rectal artesunate and referral completion of children with signs of severe malaria.

⇒ The association of rectal artesunate administration with referral completion was context specific.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The implementation of prereferral rectal artesunate should be accompanied by a monitoring of referral completion in the target population.

INTRODUCTION

Rectal artesunate (RAS) is a potentially life-saving prereferral treatment for children presenting at the primary healthcare level with suspected severe malaria.[1] Current guidelines require that children who received RAS be referred immediately to a health

facility where comprehensive management of severe malaria can be provided.[2] However, the rapid improvement of a child's condition after the administration of RAS may result in children not being taken to a referral health facility (RHF), where appropriate treatment is available.[3 4]

According to WHO guidelines, appropriate postreferral treatment of severe malaria consists of an intramuscular or intravenous antimalarial for at least 24 hours followed by a full course of an oral artemisinin-based combination therapy (ACT) and accompanied by the management of clinical complications.[5] Previous studies on RAS and referral defined referral completion as going to the nearest health facility, irrespective of the facility's capacity to treat severe malaria.[3 6–10] In the case of children first treated with RAS by a community health worker (CHW), this may be a primary health centre (PHC) that lacks the capacity to manage a severe malaria episode. In view of improving the case management of such children, more evidence is needed to understand the pathways by which children with suspected severe malaria reach a competent and capacitated healthcare provider and whether referral completion is impacted by the administration of RAS.

There is evidence that children who received prereferral treatment were less likely to complete referral than children without treatment prior to referral.[11 12] However, this kind of evidence for RAS as a prereferral treatment is scarce. Most previous quantitative studies on RAS and referral completion did not compare RAS users versus non-RAS users,[8–11 13] and, thus, did not estimate the potential effect of RAS administration on referral completion. Only one observational study tested for non-inferiority of referral completion among children receiving RAS compared with children not receiving RAS.[6] The authors concluded non-inferiority because the predefined margin of 15% was not reached; however, referral completion in RAS users (84%) was lower than in non-RAS users (94%). In addition, the analysis did not control for other factors influencing referral completion. Factors that have previously been shown to influence referral completion are household dynamics and priorities, illness severity, the type of referring provider, the performance and result of diagnostic tests prior to referral, health workers' communication skills, distance to the RHF, referral and treatment costs and the perceived quality of the RHF.[3 6–8 11–16]

The Community Access to Rectal Artesunate for Malaria (CARAMAL) project included an observational study accompanying the implementation of RAS in the Democratic Republic of the Congo (DRC), Nigeria and Uganda and is described in detail in a companion paper.[17] The training provided to CHWs and staff of PHCs during the roll-out of RAS emphasised the need to refer severely sick children to an appropriate and recognised RHF capable of managing the child's severe condition, rather than to the nearest or next-higher level provider. This manuscript aimed to assess referral completion of children with suspected severe malaria and its relationship with RAS implementation and administration, taking into consideration other factors influencing referral completion. The key study results are described by Hetzel *et al*[18] and the treatment patterns in the RHFs are described by Signorell *et al*[19]

METHODS

Study design

This observational study followed the implementation of prereferral RAS in three study areas in DRC, Nigeria and Uganda. Local health authorities in collaboration with UNICEF trained community-based providers on the use and administration of RAS. Community-based providers enrolled children under 5 years of age with fever and danger signs according to the national integrated community case management (iCCM, in the case of CHW) or integrated management of childhood illness (IMCI, in the case of PHC) guidelines. All eligible children were followed up 1 month after enrolment by dedicated research staff.

The study period covered approximately 10 months before the implementation of RAS (pre-roll-out: May 2018–February 2019) and 17 months thereafter (post-roll-out: March 2019–August 2020).

Study setting

The study was conducted in three districts in Uganda (Kole, Oyam and Kwania), three local government areas (LGA) in Adamawa State in Nigeria (Fufore, Song, Mayo-Belwa) and three health zones in the DRC (Kenge, Kingandu, Ipamu). The overall study population was 2.5 million of which 476 000 (19%) were children under 5 years. Further details are provided elsewhere.[17]

The public health system in the study areas consisted of several levels of community-based providers and at least one level of RHFs (table 1). Community-based providers implementing prereferral RAS included CHWs and PHCs. In the study health zones in DRC, CHWs were located in communities with no formal provider within a distance of 5 km. In the study of LGAs in Nigeria, CHWs were located in communities that were more than 5 km away from a public health facility, or the community was hard to reach due to bad road conditions or natural barriers like rivers or mountains. In the study districts in Uganda, there were two CHWs per village irrespective of the presence of other formal healthcare providers.

According to national policies, community-based providers should refer severely ill children to the nearest higher level healthcare provider. In the case of CHWs, these are often PHCs (eg, in Uganda, a Village Health Team may refer a child to a Health Centre II). During RAS roll-out, community-based providers who were trained in the administration of prereferral RAS were instructed to refer children immediately to a designated RHF. The importance of speedy referral was emphasised in the training. Simultaneously, UNICEF implemented

Table 1 Local names and numbers of community health worker, primary health centres and referral health facilities in 2018, by country

	DRC		Nigeria		Uganda	
	Name	N	Name	N	Name	N
Community health worker	*Site de Soins Communautaire* (Community Care Site)	42	Community oriented resource person	500	Village health team	5100
Primary health centre	*Poste de Santé* (Health Post) *Centre de Santé* (Health Centre)	152	Health post Primary health centre	77	Health centre II	30
Referral health facility	*Centre de Santé de Référence* (Referral Health Centre) and *Hôpital Général de Référence* (General Referral Hospital)	19	Cottage hospital	3	Health centre III Health centre IV hospital	20

DRC, Democratic Republic of the Congo.

behaviour change communication campaigns that informed caregivers about the benefits of RAS and the importance of referral completion on billboards, posters and leaflets. Additionally, CHWs conducted home visits, community dialogues were held, and radio messages were aired. In Uganda and DRC, there were no interventions in place to support referral to an RHF. In Nigeria, an Emergency Transport System for severely ill children was introduced in July 2019, shortly after the implementation of RAS. The Emergency Transport System provided free transport to referral facilities.

Data collection

Local research partners established a patient surveillance system for the enrolment and follow-up of children with suspected severe malaria presenting to CHWs or PHCs in DRC and Nigeria and to CHWs in Uganda. Children were enrolled if they were under 5 years, had a history of fever and at least one danger sign for which RAS is indicated as per national iCCM and IMCI guidelines. On enrolment, community-based providers conducted a malaria rapid diagnostic test (mRDT) for study purposes. After referring the child to a higher level provider, the enrolling provider reported the case to the local study office where eligible children were recorded in a central case register. In Nigeria and Uganda, this contact happened via telephone. In DRC, community-based providers were regularly visited by CARAMAL research staff to record provisionally enrolled children in the central case register. Dedicated CARAMAL staff were stationed in RHFs in the study area to record the postreferral management of referred children who were admitted for treatment. CARAMAL research staff scheduled an interview 28 days after enrolment. Deceased children were followed up 2 months after enrolment to respect the mourning period. At the follow-up visit, caregivers or other knowledgeable family members provided information on signs and symptoms, treatment-seeking history, diagnosis and treatment during the child's illness episode. The interviewer also recorded the geocoordinates of the home location of the child. Additional information on the child's condition and administered treatment on enrolment was obtained from the enrolling provider. In Uganda and DRC, the reason for not administering RAS was collected from a subsample of children in the post-RAS phase.

Data were collected electronically on tablets with Open Data Kit (ODK) Collect (https://opendatakit.org/). During admission, CARAMAL research staff at RHFs recorded information on case management on paper forms before entering it into ODK Collect. The password-protected ODK Aggregate server was hosted at the Swiss Tropical and Public Health Institute in Switzerland.

Outcomes and explanatory variables

The primary outcome of this analysis was referral completion, defined as a child being brought to one of the designated RHFs at any stage during the treatment seeking process, after seeing a community-based provider, as reported by the caregiver or by CARAMAL staff stationed at the RHF. Secondary outcomes included going to any other public provider after seeing a community-based provider and going to a provider outside of the public health system after seeing a community-based provider. A further secondary outcome was timely referral completion defined as reaching an RHF on the same or next day after enrolment. The number of days between enrolment and reaching an RHF was either calculated as the difference between the enrolment date and the date of admission at an RHF or obtained from the treatment-seeking narrative as reported by the caregiver during follow-up.

The main exposures of interest were the RAS implementation phases (pre-roll-out vs post-roll-out) and prereferral RAS administration in the post-roll-out phase. To assess these effects, we grouped children into three study groups: (1) pre-RAS, (2) RAS non-users in the post-RAS phase and (3) RAS users in the post-RAS phase. We accounted for age and gender of the child and the interviewed caregiver and the child's place of residence (health zone/LGA/district). The severity as perceived by the caregiver and the presence of a danger sign involving

the central nervous system (CNS; convulsions, unusually sleepy or unconscious) were proxies for disease severity. Additional factors considered included the mRDT result at enrolment, the type of community-based provider (CHW vs PHC), the season, day of enrolment (workday vs weekend), enrolment during the COVID-19 pandemic (1 April 2020 or later), treatment-seeking delay between the onset of illness and going to the enrolling provider, the means of transport to enrolling provider, travel time between home and nearest RHF, and the administration of home treatment before presentation to enrolling provider.

To calculate the travel time between the home of the child and the nearest RHF, we used the Malaria Atlas Project friction surface 2015 with a 100 m × 100 m resolution.[20] The calculation was done in RStudio[21] using the method described by Bertozzi-Villa.[22] Geolocations of RHFs were obtained from the CARAMAL Health Care Provider Surveys for RHFs within the study area and from Maina *et al*[23] for RHFs surrounding the study area. All geolocations were verified using Google Maps[24] and official government sources, where applicable.[25 26]

Statistical analysis

For each country, we used a logistic regression model to estimate the association of the implementation of RAS and RAS administration with referral completion. For children completing referral, we used logistic regression models to estimate the association between RAS implementation and administration and referral timeliness. All models included the enrolling PHC or CHW as random effects to account for clustering at that level. Exposure variables were selected based on rational grounds prior to analysis and included in the final model irrespective of their level of significance. Variables to test for interactions were chosen *a priori*. The interactions included in the final model were significant at the 5% level. We did not account for time trends other than the effects of the implementation of RAS, the rainy season and the COVID-19 pandemic. However, we conducted sensitivity analyses to test whether the effect of RAS implementation and administration on referral completion was sensitive to the effects of time. Observations with missing values for referral completion were excluded from the regression analysis. Statistical analyses were performed in Stata SE V.16.1.[27]

Ethics

The community-based providers informed caregivers about the CARAMAL study prior to enrolment and caregivers gave oral preconsent to be contacted for a follow-up interview. We obtained written consent from all caregivers of provisionally enrolled children either at the RHF or before the follow-up interview 28 days after enrolment.

Patient and public involvement

Patients and the public were not involved in the development of the research question and outcome measures, the design and conduct of the study.

RESULTS

Study population

Between May 2018 and August 2020, community-based providers provisionally enrolled 8365 children (online supplemental file 1). The study team successfully followed up 7593 (91%) children and obtained informed consent. Of those, 6505 (78%) children fulfilled all inclusion criteria, of which 6449 had a known referral status (77%). The majority of included children were enrolled after the implementation of RAS (n=4396, 68%). Particularly in DRC, the sample receiving RAS in the post-RAS phase was substantially larger (N=1548) compared with the other two study groups (pre-RAS: N=368; post-RAS non-users: N=188) (table 2). In Nigeria, the numbers in the study groups were balanced. In Uganda, the number of children enrolled in the pre-RAS phase (N=1479) was comparable to the number of children receiving RAS in the post-RAS phase (N=1631); however, the number of children not receiving RAS in the post-RAS phase was substantially smaller (N=635).

In Uganda, the reason for not administering RAS was recorded for 300 children in the post-RAS phase. The single most important reason was stock-out of RAS (87%). In some cases, the CHWs did not administer RAS because they kept the suppository for more severe cases (9%). In DRC, where most children received RAS in the post-RAS phase, the subsample was too small (N=18) to make valid assumptions about the reasons for not administering RAS.

Within each country, the age and gender distribution were similar among children enrolled in the pre-RAS phase, RAS users and non-users in the post-RAS phase. In Nigeria, there were fewer children under 1 year than in the other countries. Danger signs involving the CNS were most common in Uganda followed by Nigeria and DRC. In all countries, more than 90% of eligible children tested positive for malaria at enrolment. In DRC, eligible children were almost exclusively enrolled by PHCs (95%), while in Uganda, all children were enrolled by CHWs. In Nigeria, a higher proportion of children was enrolled by CHWs in the pre-RAS phase (72%) compared with the post-RAS phase (42%). Enrolment in PHCs started later because of a strike by PHC health workers at the beginning of the study. In the post-RAS phase, between 19% (Uganda) and 30% (Nigeria) of the children were enrolled during the COVID-19 pandemic. In all countries, the proportion of children receiving RAS was higher during the COVID-19 pandemic.

Referral completion

In DRC, overall, 1408 (67%) children completed referral to a designated RHF. Few children went to another public

Table 2 Study population characteristics by country and study group

Background characteristic	DRC			Nigeria			Uganda		
		Post-RAS			Post-RAS			Post-RAS	
	Pre-RAS	No RAS	RAS	Pre-RAS	No RAS	RAS	Pre-RAS	No RAS	RAS
N	**368%**	**188%**	**1548%**	**206%**	**183%**	**211%**	**1479%**	**635%**	**1631%**
Female	47.0	45.7	46.8	38.8	35.5	43.1	46.0	48.2	46.9
Age (years)									
0	20.4	23.4	19.2	12.6	9.8	12.8	17.4	20.2	17.7
1	31.5	34.6	28.6	25.7	29.5	26.5	27.7	29.4	29.5
2	21.5	21.8	22.4	27.7	29.0	28.4	23.9	22.8	24.0
3	12.2	10.6	15.7	21.8	16.9	20.4	18.7	18.6	18.4
4	14.4	9.6	14.1	12.1	14.8	11.8	12.3	9.0	10.4
Study area (DRC/Nigeria/Uganda)									
Ipamu/Mayo-Belwa/Kole	22.6	23.9	36.4	27.7	49.2	49.3	65.2	60.6	24.5
Kenge/Fufore/Oyam	42.7	37.2	34.8	57.3	37.7	27.5	16.5	28.5	34.7
Kingandu/Song/Kwania	34.8	38.8	28.7	15.0	13.1	23.2	18.3	10.9	40.8
Danger signs									
Unusually sleepy or unconscious	44.0	28.2	23.8	68.0	66.7	61.6	65.0	87.6	91.7
Not able to drink or feed	61.1	71.8	47.9	70.4	60.7	54.5	62.5	82.5	78.1
Vomiting everything	14.1	10.6	26.0	82.5	71.6	56.9	78.3	72.1	65.2
Convulsions	56.0	45.7	61.7	55.3	64.5	82.9	39.8	25.5	52.0
CNS involvement*	70.9	59.0	68.1	81.1	79.8	89.1	78.6	90.9	96.9
Positive malaria test at enrolment	82.3	92.0	98.7	95.1	95.1	93.8	97.4	98.3	99.4
Enrolment location									
Community health worker	6.0	2.1	4.5	71.8	41.5	43.1	100.0	100.0	100.0
Primary health centre	94.0	97.9	95.5	28.2	58.5	56.9	0.0	0.0	0.0
Enrolled during rainy season†	90.5	39.9	47.6	64.6	78.7	80.1	61.7	91.2	52.9
Enrolled on a workday	78.8	68.6	74.8	78.2	85.8	82.9	74.9	76.7	73.0
Enrolled during COVID-19 pandemic	0.0	8.0	29.1	0.0	13.1	44.1	0.0	9.3	22.3
Delay to enrolling provider									
0–1 days	26.1	27.7	33.5	33.0	31.1	34.1	48.5	56.7	64.8
>1 day	60.1	68.1	63.8	47.1	57.4	59.2	49.8	42.0	34.4
Missing	13.9	4.3	2.7	19.9	11.5	6.6	1.7	1.3	0.8
Transport to enrolling provider									
No vehicle	72.6	79.3	82.4	56.8	45.4	47.9	91.8	91.8	93.3
Vehicle	12.5	15.4	15.0	25.7	43.2	46.0	7.7	7.2	6.1
Missing	14.9	5.3	2.6	17.5	11.5	6.2	0.5	0.9	0.6
Time to referral health facility (min)									
0–<15	34.0	39.9	39.1	18.0	18.0	16.1	59.6	57.8	45.9
15–<30	17.7	13.3	15.0	12.1	15.3	16.1	34.0	37.6	43.8
30–<60	20.9	11.2	15.4	19.9	26.8	28.0	5.0	4.6	10.2
≥60	19.3	6.9	9.3	49.5	37.2	36.5	0.1	0.0	0.0
Missing	8.2	28.7	21.2	0.5	2.7	3.3	1.2	0.0	0.0
Child perceived fatally ill	29.9	31.9	24.2	29.6	22.4	28.0	43.3	43.3	45.5
Missing	0.3	0.5	1.0	0.0	1.1	1.4	0.5	0.0	0.2
Home treatment	65.2	76.1	59.9	24.8	47.5	39.3	15.2	13.9	9.9
Missing	0.0	0.0	0.0	0.0	1.1	0.9	0.0	0.0	0.0

*Convulsions, unusually sleepy or unconscious.
†DRC: October–April; Nigeria: May–October; Uganda: April–October.
CNS, central nervous system; RAS, rectal artesunate.

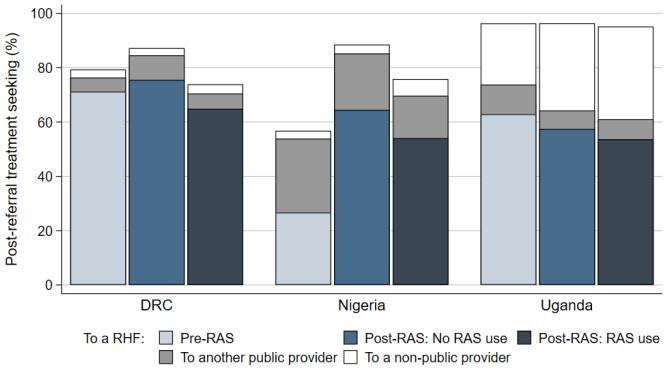

Figure 1 Post-referral treatment seeking from a referral health facility (RHF), from other public providers and from non-public providers, for children enrolled before the implementation of rectal artesunate (pre-RAS), and after the implementation of RAS (post-RAS) for RAS non-users and RAS users, by country.

provider (6%) or to any other provider (3%). In Nigeria, 287 (48%) children completed referral to a designated RHF. An additional 21% of the children went to another public provider and only 4% of the children went to a non-public provider. In Uganda, 2170 (58%) of the children completed referral to the designated RHFs. Going to another public provider was infrequent (9%), but 29% of the children in Uganda were brought to providers outside of the public health system.

In all countries, referral completion to an RHF was slightly lower among RAS users compared with RAS non-users in the post-RAS phase (figure 1, table 3 and table 4). In DRC and Uganda, referral completion in the post-RAS phase was comparable to referral completion in the pre-RAS phase. Meanwhile, in Nigeria, referral completion increased from the pre-RAS to the post-RAS phase. The difference between the pre-RAS and post-RAS phase was mainly driven by PHC enrolments being substantially more likely to complete referral to an RHF than CHW enrolments, in combination with an increase in the number of PHC enrolments in the post-RAS phase (figure 2).

In both DRC and Nigeria, going to any other provider than an RHF was uncommon for PHC enrolments (figure 2); but seemed more common for CHW enrolments who frequently went to a public provider other than a designated RHF. In Uganda, children rarely went to another public provider but tended instead to go to a private provider, compensating the lower referral completion to an RHF in the two post-RAS study groups (figure 1).

In DRC and Uganda, referral completion was lower in the post-RAS phase compared with the pre-RAS phase after adjusting for other factors, irrespective of whether children had received RAS (table 3). The opposite occurred in Nigeria, where referral completion in the post-RAS phase irrespective of RAS use was higher compared with the pre-RAS phase (table 4).

When taking RAS non-users in the post-RAS phase, as a reference, the odds of completing referral did not significantly differ between children not receiving RAS and children receiving RAS in DRC (adjusted OR (aOR)=1.39, 95% CI 0.82 to 2.35) and Uganda (aOR=0.90, 95% CI 0.70 to 1.16). In Nigeria, the same was true for children enrolled by a CHW (aOR=2.51, 95% CI 0.76 to 8.24); however, among children enrolled by a PHC, those who had received RAS were significantly less likely to complete referral than those not receiving RAS in the post-RAS phase (aOR=0.18, 95% CI 0.05 to 0.71).

Besides RAS implementation and RAS administration, we found other factors significantly associated with referral completion. In all countries, increasing travel time to the RHF had a negative effect on referral completion. In DRC and Nigeria, children were more likely to complete referral if they were referred by a PHC compared with a CHW (not applicable in Uganda). Other factors that had a positive effect on referral completion included being perceived fatally ill by the caregiver (DRC), having received home treatment (DRC) or being enrolled on a workday (Uganda). Factors with a negative effect on referral completion included having a CNS danger sign (DRC) or being enrolled during the COVID-19 pandemic (Nigeria).

The adjusted ORs did not differ substantially from the unadjusted estimates except for the effect of the malaria test result in DRC and being enrolled by a PHC in Nigeria. Unadjusted estimates are provided in online supplemental file 2.

The sensitivity analyses showed that the effects of RAS implementation and administration were sensitive to assumptions about the underlying time trends in DRC and Uganda. If a linear time trend for the outcome variable was additionally included, then in DRC, there was no significant difference in referral completion between the pre-RAS and post-RAS phases if the model accounted for time in months. In Uganda, referral completion significantly increased with the implementation of RAS but decreased at a higher rate thereafter. In Nigeria, the results did not change if the model was adjusted for time in trimesters. However, the data were not sufficient to estimate time trends and the contributions of time and RAS could not be distinguished well.

Referral timeliness

Of the 3865 children that completed referral to an RHF, data on the timeliness of referral completion weere available for 3598 children (93%) (online supplemental file 1). Timely referral completion to an RHF on the same or next day after seeing a community-based provider was 76% in DRC, 86% in Nigeria and 92% in Uganda. In all countries, timely referral was highest among children receiving RAS in the post-RAS phase; however, the differences between study groups were rather small (figure 3). After adjusting for other factors, children in Uganda receiving RAS in the post-RAS phase were significantly more likely to complete referral on time than

Table 3 Estimated associations between selected factors and referral completion in DRC and Uganda

	DRC					Uganda				
	N§	Referral completion (%)	Adjusted OR*	95% CI	P value	N§	Referral completion (%)	Adjusted OR*	95% CI	P value
All	2104	66.9				3745	57.9			
Study group										
Pre-RAS	368	71.2	Ref.			1479	62.9	Ref.		
Post-RAS										
No RAS use	188	75.5	0.34	0.18 to 0.66	0.001	635	57.5	0.80	0.63 to 1.01	0.06
RAS use	1548	64.9	0.48	0.30 to 0.77	0.002	1631	53.6	0.72	0.58 to 0.88	0.002
Enrolment location										
CHW	96	43.8	Ref.			3745	57.9			
PHC	2008	68.0	4.85	1.22 to 19.25	0.02	0	NA	NA		
CNS danger sign†										
No	678	78.5	Ref.			425	62.8	Ref.		
Yes	1426	61.4	0.58	0.41 to 0.82	0.002	3320	57.3	0.80	0.61 to 1.04	0.09
Enrolled during rainy season‡										
No	959	69.3	Ref.			1392	55.5	Ref.		
Yes	1145	64.9	0.77	0.56 to 1.07	0.12	2353	59.4	1.15	0.97 to 1.38	0.11
Enrolled on a workday										
No	527	69.3	Ref.			959	53.8	Ref.		
Yes	1577	66.1	0.91	0.65 to 1.29	0.60	2786	59.4	1.19	1.00 to 1.41	0.05
Enrolled during COVID-19 pandemic										
No	1638	66.7	Ref.			3323	57.8	Ref.		
Yes	466	67.8	1.15	0.78 to 1.70	0.48	422	58.8	0.90	0.69 to 1.19	0.48
Delay to enrolling provider										
0–1 days	667	60.3	Ref.			2134	56.8	Ref.		
>1 day	1336	68.5	1.07	0.77 to 1.49	0.69	1565	59.1	1.14	0.97 to 1.34	0.12
Missing	101	90.1	3.33	0.86 to 12.83	0.08	46	71.7	1.11	0.43 to 2.86	0.83
Transport to enrolling provider										
No vehicle	1691	63.0	Ref.			3462	57.8	Ref.		
Vehicle	307	81.8	1.08	0.66 to 1.79	0.75	260	57.7	1.06	0.78 to 1.42	0.72
Missing	106	86.8	4.80	1.37 to 16.84	0.01	23	78.3	3.31	0.78 to 14.06	0.11
Time to referral health facility (min)										
0–<15	806	82.9	Ref.			1998	67.5	Ref.		
15–<30	322	72.0	1.12	0.65 to 1.95	0.68	1457	47.5	0.72	0.58 to 0.89	0.003
30–<60	336	67.9	0.80	0.46 to 1.40	0.44	270	42.6	0.55	0.39 to 0.79	0.001
≥60	228	35.1	0.46	0.24 to 0.89	0.02	2	0.0	NA		
Missing	412	48.5	0.87	0.52 to 1.46	0.60	18	77.8	1.88	0.53 to 6.67	0.33
Perceived severity										
Not fatal	1542	63.5	Ref.			2078	56.8	Ref.		
Fatal	545	75.8	1.86	1.28 to 2.71	0.001	1657	59.4	1.11	0.94 to 1.30	0.21
Missing	17	94.1	16.14	0.61 to 429.60	0.10	10	50.0	0.80	0.20 to 3.19	0.75
Home treatment										
No	793	56.1	Ref.			3271	57.4	Ref.		
Yes	1311	73.5	1.43	1.03 to 1.99	0.03	474	62.0	1.10	0.87 to 1.39	0.41
Missing	0	NA	NA			0	NA	NA		

*OR additionally adjusted for child sex, child age, caregiver sex, caregiver age, location of residence (health zone, district) and malaria test result.
†Danger signs involving the CNS: convulsions, unusually sleepy or unconscious.
‡DRC: October–April; Uganda: April–October.
§Denominator.
CHW, community health worker; CNS, central nervous system; DRC, Democratic Republic of the Congo; PHC, primary health centre; RAS, rectal artesunate.

Table 4 Estimated associations between selected factors and referral completion in Nigeria

	Nigeria				
	N*	Referral completion (%)	Adjusted OR**	95% CI	P value
All	600	47.8			
Study group by enrolment location					
CHW					
Pre-RAS	148	6.1	Ref.		
Post-RAS					
No RAS use	76	21.1	3.97	1.07 to 14.75	0.04
RAS use	91	26.4	9.95	2.71 to 36.58	<0.001
PHC†					
Pre-RAS	58	79.3	Ref.		
Post-RAS					
No RAS use	107	95.3	35.09	6.52 to 188.75	<0.001
RAS use	120	75.0	6.45	1.62 to 25.67	0.01
Enrolment location					
CHW	315	15.6	Ref.		
PHC†	285	83.5	19.79	2.97 to 131.71	0.002
CNS involvement‡					
No	99	33.3	Ref.		
Yes	501	50.7	0.48	0.17 to 1.38	0.17
Enrolled during rainy season§					
No	154	50.6	Ref.		
Yes	446	46.9	0.70	0.29 to 1.67	0.42
Enrolled on a workday					
No	107	30.8	Ref.		
Yes	493	51.5	0.74	0.31 to 1.76	0.50
Enrolled during COVID-19 pandemic					
No	483	49.5	Ref.		
Yes	117	41.0	0.09	0.03 to 0.26	<0.001
Delay to enrolling provider					
0–1 days	197	45.7	Ref.		
>1 day	327	47.1	1.64	0.77 to 3.52	0.20
Missing	76	56.6	3.53	1.03 to 12.09	0.04
Transport to enrolling provider					
No vehicle/missing¶	371	33.7	Ref.		
Vehicle	229	70.7	0.82	0.32 to 2.10	0.68
Time to referral health facility (min)					
0–<15	104	81.7	Ref.		
15–<30	87	71.3	0.48	0.13 to 1.73	0.26
30–<60	149	55.7	0.23	0.07 to 0.77	0.02
≥60	247	19.4	0.06	0.02 to 0.22	<0.001
Missing	13	69.2	0.13	0.01 to 1.84	0.13
Perceived severity					
Not fatal	434	48.8	Ref.		
Fatal	161	44.7	0.63	0.30 to 1.32	0.23
Missing	5	60.0	1.23	0.01 to 153.00	0.93

Continued

Table 4 Continued

	Nigeria				
	N*	Referral completion (%)	Adjusted OR**	95% CI	P value
Home treatment					
No/missing¶	379	43.8	Ref.		
Yes	221	54.8	1.08	0.54 to 2.16	0.82

*OR additionally adjusted for child sex, child age, caregiver sex, caregiver age, location of residence (LGA) and malaria test result.
†Adjusted for LGA. OR shown for Mayo-Belwa. ORs for Fufore and Song are higher.
‡Danger signs involving the CNS: convulsions, unusually sleepy or unconscious.
§May–October.
¶Observations with missing values added to reference category because no meaningful OR could be computed due to the data structure (missing values in other covariates).
**Denominator.
CHW, community health worker; CNS, central nervous system; PHC, primary health centre; RAS, rectal artesunate.

children in the pre-RAS phase (OR=1.81, 95% CI 1.17 to 2.79). Other comparisons between study groups were not significant in any of the countries. Complete tables with denominators and regression results are presented in online supplemental file 3.

DISCUSSION

After the administration of prereferral RAS, current guidelines recommend referral completion to a health facility where intramuscular or intravenous treatment is available.[5] Findings from previous studies on RAS and referral completion were mostly reassuring; however, the effect of RAS on referral completion was either not adjusted for other factors[6] or did not compare RAS users to non-users.[8–11 13] Additionally, none of the studies took into consideration that the nearest health facility might not have the capacity of administering parenteral antimalarial treatment. The CARAMAL Project for the first time provides adjusted estimates of the effect of RAS on referral completion to an RHF at which, according to national policy, appropriate postreferral treatment is available. Postreferral treatment with an injectable antimalarial followed by a full course of ACT ensures that children are effectively treated for severe malaria, and RAS (and parenteral artemisinin) is not applied as a monotherapy, thereby reducing the risk of the development and selection of artemisinin-resistant parasites.[5]

In the context of the large-scale implementation of RAS, our study found a negative association between RAS and referral completion. In DRC and Uganda, referral completion was lower in the post-roll-out phase compared with the pre-roll-out phase. In Nigeria, the opposite was the case. However, in Nigeria, children who were administered RAS in a PHC were less likely to complete referral to an RHF than children who did not receive RAS. Referral completion by children attending a PHC in Nigeria and DRC was consistently higher when compared with the

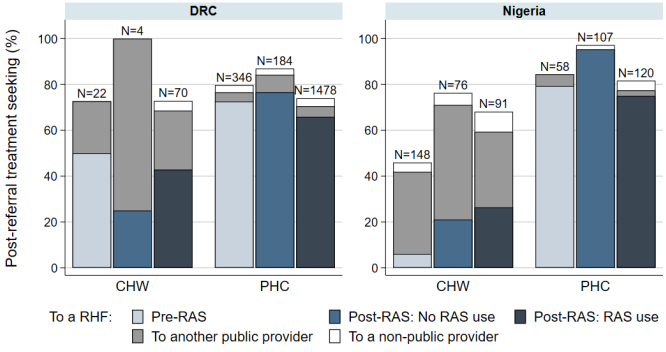

Figure 2 Post-referral treatment seeking from a referral health facility (RHF), from other public providers and from non-public providers for children enrolled before the implementation of rectal artesunate (pre-RAS), and after the implementation of RAS (post-RAS) for RAS non-users and RAS users, by enrolment location, in DRC and Nigeria. CHW, community health worker; DRC, Democratic Republic of the Congo; PHC, primary health centre.

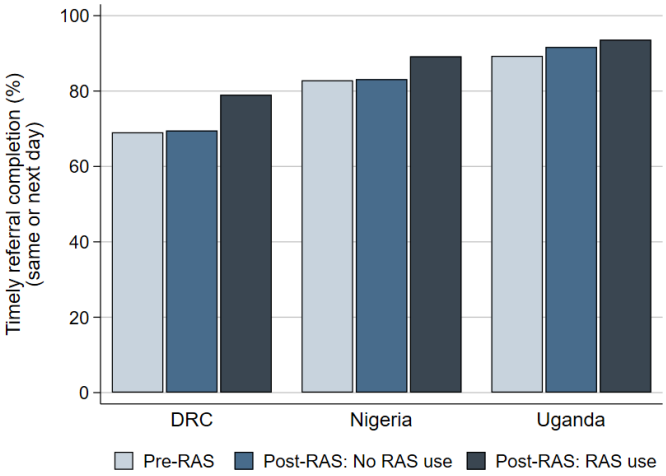

Figure 3 Timely referral completion on the same or next day after referral by a community-based provider, from all patients completing referral to a referral health facility, for children enrolled before the implementation of rectal artesunate (pre-RAS), and after the implementation of RAS (post-RAS) for RAS non-users and RAS users, by country. DRC, Democratic Republic of the Congo.

referral completion of children attending a CHW (not applicable in Uganda). In all countries, children living a greater distance from an RHF (measured in the time it would take to travel to the facility) were significantly less likely to complete referral than those living in the vicinity of the facility. In all countries, the majority of children who completed referral to an RHF did so on the same or next day after being referred.

The findings of this study raise legitimate concerns that the roll-out of RAS may lead to lower referral completion in children who were administered prereferral RAS. This was most notable among children enrolled in PHCs in Nigeria, and also the results from DRC may suggest a negative association between RAS and referral completion. In DRC, the comparatively small number of RAS non-users limited the validity of the comparison between RAS users and non-users in the post-roll-out phase. Therefore, the negative association between RAS implementation and referral completion may indicate that children who received RAS were at higher risk of not completing referral; even though other causal links cannot be excluded. The reason for a decrease in referral completion after RAS use is most likely the rapid improvement of children after RAS administration, a result of the fast reduction of the parasite to blood concentration and the drug's antipyretic effect.[28–31] Considering that treatment seeking is often delayed due to lack of transport and money,[32–34] the child's condition may have improved in the meantime. In such a situation, a caregiver is likely to balance between the referral recommendation and priorities at home, in addition to expenses for transport and those that would be incurred at the RHF.[3] Obviously, such a practice raises the concern that children may not receive the appropriate postreferral treatment with potentially fatal consequences.

Measures to improve referral completion must take into consideration the actual capacity of RHFs to provide appropriate case management for severe malaria. As opposed to previous studies, this study considered referral to be completed only if the patient arrived at an RHF with the capacity to manage severe malaria cases. However, an analysis of the quality of care at RHFs in the CARAMAL study areas found that the treatment of children with severe malaria was often inadequate.[19] Meanwhile, some children sought postreferral treatment from a lower level public or from a non-public provider. Considering that referral completion did not improve the health outcome of children enrolled in the CARAMAL study in DRC and Uganda,[18] sufficient treatment may have been provided by non-RHF providers.[35] It is also possible that less severely sick children recover faster and are hence less likely to be brought to an RHF after prereferral RAS treatment. Therefore, children with suspected severe malaria first attending a community-based provider may not always require treatment at the level of RHFs. However, recognising such children with a more moderate form of severe malaria remains a challenge.

The finding that a substantial proportion of children (33%–52%) did not complete referral emphasises the need to address referral-related barriers at all levels: for example, sensitising caregivers, properly training community-based healthcare providers, facilitating access to and increasing trust in RHFs. Such a package of supportive interventions accompanying the roll-out of RAS in Zambia has previously been shown to reduce the mortality of children with severe malaria.[36] In a trial conducted by Gomes *et al*,[1] RAS had a protective effect in the context of high completion of referral (though not necessarily to a RHF in the African sites). In the CARAMAL study in Nigeria, the implementation of an Emergency Transport System most likely increased referral completion, and referral completion significantly improved the health outcomes of children with suspected severe malaria in this country. The available evidence strongly indicates that community-based programmes should always be accompanied by measures strengthening referral.

Irrespective of the effort to strengthen referral, it is important to acknowledge that some caregivers to children may delay or not complete referral. Therefore, the training materials and referral guidelines for community-based providers need to emphasise the importance of a close follow-up of severely sick children, if necessary at their home. If referral cannot be completed or is refused by the caregiver, the treatment with prereferral drugs should be continued. Such a recommendation already exists for RAS until oral treatment with an ACT is tolerated.[2] Similarly, the WHO recommends that CHWs continue administering amoxicillin to children with pneumonia with chest in-drawing if referral is not feasible.[37] Sufficient stocks of prereferral drugs are, therefore, essential for providing adequate care to children unable to complete referral.

Referral completion to an RHF was a problem particularly among CHW enrolments in DRC and Nigeria. Unlike in Uganda, CHWs in these two countries are placed in especially hard-to-reach areas. In our analyses, we accounted for difficulties in geographical access to an RHF (availability of transport and travel time to RHF), but we may have missed additional barriers to accessing an RHF. Another explanation could be that children attending a PHC are more severely ill than children attending a CHW.[38] Caregivers may be more likely to make increased efforts to reach the first provider as well as to complete referral if the child is more severely ill. Meanwhile, irrespective of the reasons, an active follow-up of children at home seems to be particularly important in the most hard-to-reach places where referral completion is the least likely. As community programmes continue to be the preferred approach to extend health services to remote communities, the challenges associated with these hard-to-reach places need to be acknowledged in referral and treatment guidelines and the promotion of best practices.

Even though treatment-seeking practices including referral are highly contextual, some recommendations based on the results of this study can be generalised to other settings, that is, programmes implementing RAS need to consider the potential effects on referral completion. More generally, community-based programmes should be supported by measures facilitating referral completion and provide a back-up option for those children who fail to complete referral. Alternative treatment options are particularly important in hard-to-reach places.

This study has several strengths. First, it covered three different contexts with varying intensities of malaria transmission, access to healthcare and differences in the implementation of iCCM/IMCI policies.[17] Second, the study was community based and enrolled a large number of children with severe febrile illness from remote communities. Large community-based studies in far-to-reach places are mostly cross-sectional surveys that rarely capture severe illness episodes because of their low incidence and always exclude children who are deceased, resulting in a lack of understanding of severe illnesses at community level.[39] Third, the study achieved a high follow-up rate, thereby reducing the risk of selection bias.

This study comes with several limitations. First, the low enrolment numbers of children not receiving RAS in the post-roll-out phase did not allow a clear conclusion about the association between RAS administration and referral completion in DRC. Second, the enrolment strategy in Nigeria and Uganda may have introduced selection bias. The notification of enrolments from the enrolling provider to the local study office depended on a contact via mobile phone. Thus, the study may have excluded systematically children in the most remote places because of unstable network coverage. It is likely that these children would have also been the least likely to complete referral leading to an overestimation of referral completion in our study. Third, the observational design and the retrospective data collection 28 days after enrolment did not allow for direct causal inferences.

CONCLUSION

Providing prompt and appropriate healthcare to severely sick children in remote communities remains a challenge. Children in hard-to-reach places are the least likely to complete referral after seeing a community-based provider. In addition, referral completion may further be negatively affected by the administration of RAS. To ensure that community-based programmes are effectively implemented, barriers to referral completion need to be addressed at all levels. Alternative effective treatment options should be provided to children unable to complete referral.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Research Ethics Review Committee of the World Health Organization (WHO ERC, Number ERC.0003008), the Ethics Committee of the University of Kinshasa School of Public Health (Number 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 (Number 548), the Uganda National Council for Science and Technology (UNCST, Number SS 4534), and the Scientific and Ethical Review Committee of CHAI (Number 112, 21 November 2017). Participants gave informed consent to participate in the study before taking part.

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Pre-referral rectal artesunate and referral completion among children with suspected severe malaria in the Democratic Republic of the Congo, Nigeria and Uganda

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Supplementary material

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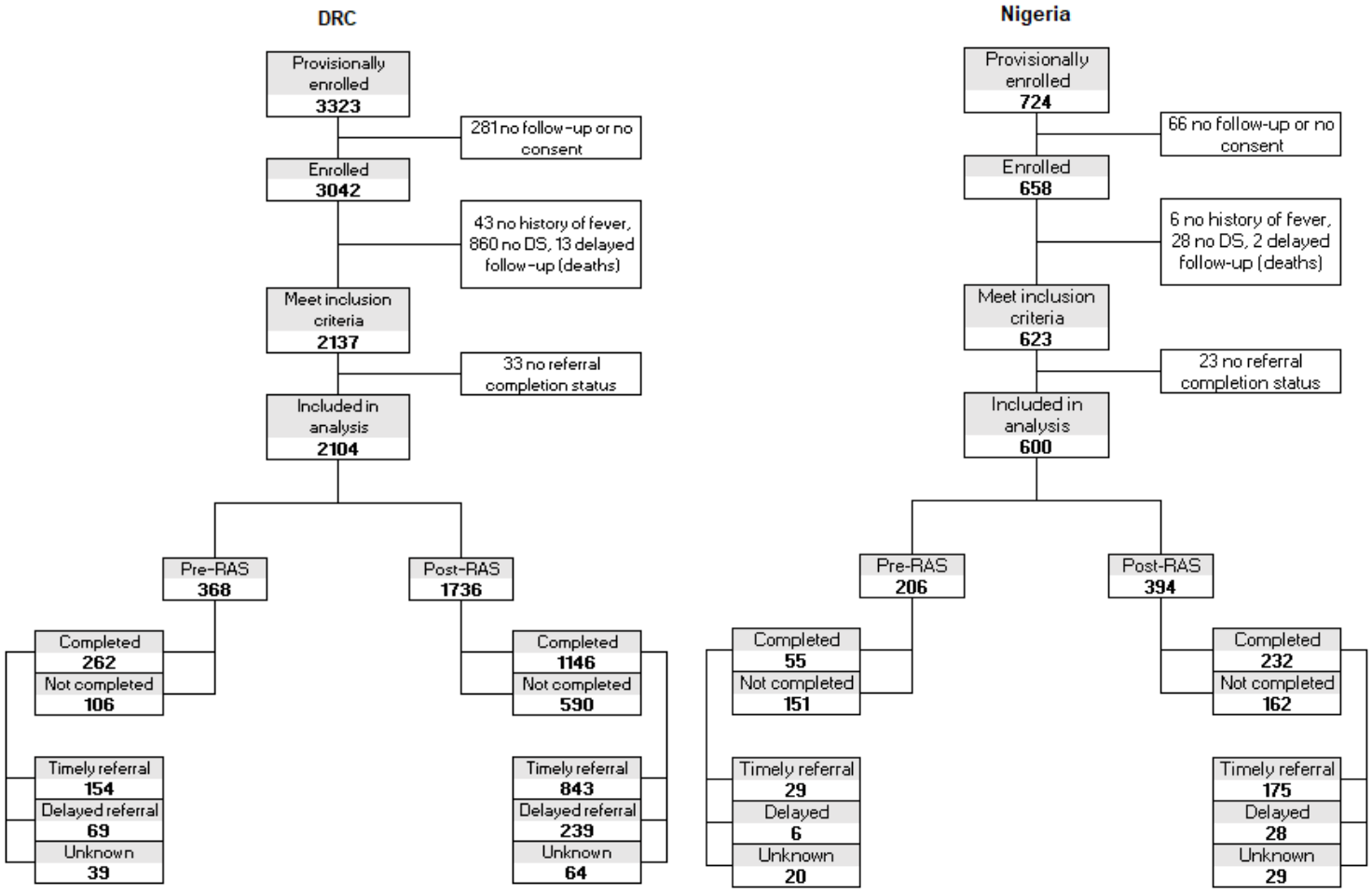
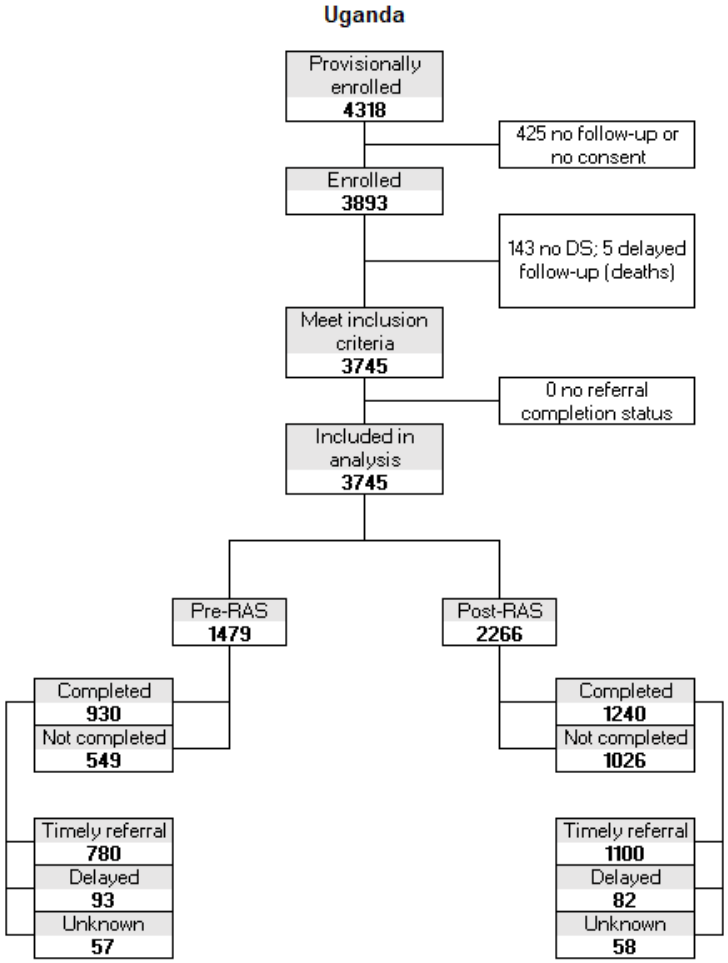
Supplement 1

Inclusion flow-charts




Uganda
Provisionally enrolled 4318
425 no follow-up or no consent
Enrolled 3893
143 no DS; 5 delayed follow-up (deaths)
Meet inclusion criteria 3745
0 no referral completion status
Included in analysis 3745
Pre-RAS 1479
Post-RAS 2266
Completed 930
Not completed 549
Completed 1240
Not completed 1026
Timely referral 780
Delayed 93
Unknown 57
Timely referral 1100
Delayed 82
Unknown 58

Supplement 2

Table S2 1. Estimated associations between child characteristics and referral completion, DRC.

				DRC					
	n	N	%	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
All	**1,408**	**2,104**	**66.9**						
Study group									
Pre-RAS	262	368	71.2	Ref.			Ref.		
Post-RAS									
No RAS use	142	188	75.5	0.42	0.23–0.77	0.005	0.34	0.18–0.66	0.001
RAS use	1,004	1,548	64.9	0.54	0.36–0.82	0.004	0.48	0.30–0.77	0.002
Child gender									
Male	735	1,121	65.6	Ref.			Ref.		
Female	673	983	68.5	0.97	0.74–1.28	0.85	1.01	0.75–1.34	0.97
Age									
0	312	416	75.0	Ref.			Ref.		
1	441	624	70.7	0.72	0.48–1.08	0.11	0.78	0.51–1.19	0.25
2	303	467	64.9	0.74	0.49–1.14	0.18	0.77	0.49–1.20	0.24
3	187	308	60.7	0.62	0.39–1.01	0.05	0.69	0.42–1.14	0.15
4	165	289	57.1	0.56	0.34–0.91	0.02	0.53	0.31–0.88	0.02
Caregiver age									
<25	176	243	72.4	Ref.			Ref.		
25–34	530	765	69.3	1.19	0.74–1.93	0.47	1.32	0.79–2.19	0.29
35–44	495	791	62.6	1.39	0.84–2.28	0.20	1.62	0.94–2.78	0.08
>=45	207	305	67.9	1.28	0.73–2.27	0.39	1.38	0.74–2.57	0.31
Missing	0	0	NA	NA			NA		
Caregiver gender									
Male	789	1,265	62.4	Ref.			Ref.		
Female	619	839	73.8	1.10	0.81–1.49	0.54	1.19	0.85–1.67	0.31
Health zone									
Ipamu	562	692	81.2	Ref.			Ref.		
Kenge	488	766	63.7	0.10	0.03–0.30	<0.001	0.16	0.05–0.49	0.001
Kingandu	358	646	55.4	0.51	0.17–1.54	0.23	0.64	0.21–1.98	0.44
CNS involvement*									
No	532	678	78.5	Ref.			Ref.		
Yes	876	1,426	61.4	0.60	0.43–0.83	0.002	0.58	0.41–0.82	0.002
Malaria test									
Negative / Not done	64	100	64.0	Ref.			Ref.		
Positive	1,344	2,004	67.1	1.46	0.77–2.74	0.24	4.02	1.87–8.60	<0.001
Enrolment location									
CHW	42	96	43.8	Ref.			Ref.		
PHC	1,366	2,008	68.0	6.09	1.51–24.57	0.01	4.85	1.22–19.25	0.02

Enrolled during rainy season**									
No	665	959	69.3	Ref.			Ref.		
Yes	743	1,145	64.9	0.97	0.73–1.28	0.82	0.77	0.56–1.07	0.12
Enrolled on a workday									
No	365	527	69.3	Ref.			Ref.		
Yes	1,043	1,577	66.1	0.93	0.67–1.28	0.65	0.91	0.65–1.29	0.60
Enrolled during Covid-19 pandemic									
No	1,092	1,638	66.7	Ref.			Ref.		
Yes	316	466	67.8	1.12	0.80–1.58	0.50	1.15	0.78–1.70	0.48
Delay to enrolling provider									
0–1 days	402	667	60.3	Ref.			Ref.		
> 1 day	915	1,336	68.5	1.33	0.98–1.79	0.06	1.07	0.77–1.49	0.69
Missing	91	101	90.1	7.87	3.08–20.10	<0.001	3.33	0.86–12.83	0.08
Transport to enrolling provider									
By foot / at home	1,065	1,691	63.0	Ref.			Ref.		
Vehicle	251	307	81.8	1.05	0.65–1.70	0.85	1.08	0.66–1.79	0.75
Missing	92	106	86.8	6.90	2.99–15.89	<0.001	4.80	1.37–16.84	0.01
Time to RHF (min)									
0–<15	668	806	82.9	Ref.			Ref.		
15–<30	232	322	72.0	1.01	0.60–1.71	0.98	1.12	0.65–1.95	0.68
30–<60	228	336	67.9	0.85	0.50–1.43	0.54	0.80	0.46–1.40	0.44
≥60	80	228	35.1	0.55	0.29–1.03	0.06	0.46	0.24–0.89	0.02
Missing	200	412	48.5	0.75	0.46–1.23	0.26	0.87	0.52–1.46	0.60
Perceived severity									
Not fatal	979	1,542	63.5	Ref.			Ref.		
Fatal	413	545	75.8	1.57	1.10–2.25	0.01	1.86	1.28–2.71	0.001
Missing	16	17	94.1	33.29	1.39–795.57	0.03	16.14	0.61–429.60	0.10
Home treatment									
No	445	793	56.1	Ref.			Ref.		
Yes	963	1,311	73.5	1.51	1.12–2.03	0.01	1.43	1.03–1.99	0.03
Missing	0	0	NA	NA			NA		

* Danger signs involving the central nervous system (CNS): convulsions, unusually sleepy or unconscious
** October-April

Table S2 2. Estimated associations between child characteristics and referral completion, Nigeria.

	Nigeria								
	n	N	%	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
All	**287**	**600**	**47.8**						
Study group									
Pre-RAS	55	206	26.7	Ref.			NA		
Post-RAS									
No RAS use	118	183	64.5	5.95	2.54–13.93	<0.001	NA		
RAS use	114	211	54.0	2.17	0.94–5.01	0.07	NA		
Child gender									
Male	177	364	48.6	Ref.			Ref.		
Female	110	236	46.6	0.67	0.37–1.23	0.20	0.58	0.29–1.17	0.13
Age									
0	28	71	39.4	Ref.			Ref.		
1	85	163	52.1	1.51	0.51–4.47	0.46	1.88	0.57–6.29	0.30
2	86	170	50.6	1.07	0.37–3.10	0.90	1.23	0.38–3.92	0.73
3	50	119	42.0	0.63	0.21–1.92	0.42	0.74	0.21–2.59	0.64
4	38	77	49.4	1.57	0.45–5.45	0.47	1.96	0.50–7.64	0.33
Caregiver age									
<25	52	93	55.9	Ref.			Ref.		
25–34	140	300	46.7	0.53	0.21–1.34	0.18	0.55	0.19–1.59	0.27
35–44	68	149	45.6	0.43	0.16–1.18	0.10	0.53	0.16–1.75	0.30
>=45	26	57	45.6	0.39	0.11–1.37	0.14	0.58	0.14–2.50	0.47
Missing	1	1	100.0	NA			NA		
Caregiver gender									
Male	96	201	47.8	Ref.			Ref.		
Female	191	399	47.9	1.88	1.00–3.54	0.05	1.35	0.61–3.00	0.46
LGA									
Mayo-Belwa	160	251	63.7	Ref.					
Fufore	84	245	34.3	0.33	0.07–1.49	0.15	NA		
Song	43	104	41.3	1.00	0.19–5.28	1.00	NA		
CNS involvement									
No	33	99	33.3	Ref.			Ref.		
Yes	254	501	50.7	0.77	0.33–1.83	0.56	0.48	0.17–1.38	0.17
Malaria test									
Negative / Not done	15	32	46.9	Ref.			Ref.		
Positive	272	568	47.9	1.45	0.35–5.94	0.61	4.31	0.69–26.75	0.12
Enrolment location									
CHW	49	315	15.6	Ref.			NA		
PHC	238	285	83.5	85.47	23.16–315.38	<0.001	NA		
Enrolled during rainy season**									
No	78	154	50.6	Ref.			Ref.		
Yes	209	446	46.9	0.64	0.32–1.29	0.21	0.70	0.29–1.67	0.42

Enrolled on a workday									
No	33	107	30.8	Ref.			Ref.		
Yes	254	493	51.5	1.48	0.67–3.27	0.33	0.74	0.31–1.76	0.50
Enrolled during Covid-19 pandemic									
No	239	483	49.5	Ref.			Ref.		
Yes	48	117	41.0	0.19	0.08–0.42	<0.001	0.09	0.03–0.26	<0.001
Delay to enrolling provider									
0–1 days	90	197	45.7	Ref.			Ref.		
> 1 day	154	327	47.1	1.35	0.71–2.58	0.36	1.64	0.77–3.52	0.20
Missing	43	76	56.6	2.27	0.80–6.44	0.12	3.53	1.03–12.09	0.04
Transport to enrolling provider									
No vehicle / missing	125	371	33.7	Ref.			Ref.		
Vehicle	162	229	70.7	1.28	0.60–2.69	0.52	0.82	0.32–2.10	0.68
Time to RHF (min)									
0–<15	85	104	81.7	Ref.			Ref.		
15–<30	62	87	71.3	0.60	0.17–2.14	0.43	0.48	0.13–1.73	0.26
30–<60	83	149	55.7	0.39	0.13–1.21	0.10	0.23	0.07–0.77	0.02
> 60	48	247	19.4	0.13	0.04–0.43	<0.001	0.06	0.02–0.22	<0.001
Missing	9	13	69.2	0.85	0.10–7.15	0.88	0.13	0.01–1.84	0.13
Perceived severity									
Not fatal	212	434	48.8	Ref.			Ref.		
Fatal	72	161	44.7	0.61	0.32–1.17	0.14	0.63	0.30–1.32	0.23
Missing	3	5	60.0	1.25	0.05–32.21	0.89	1.23	0.01–153.00	0.93
Home treatment									
No / missing	166	379	43.8	Ref.			Ref.		
Yes	121	221	54.8	1.14	0.63–2.06	0.68	1.08	0.54–2.16	0.82
Interactions									
Enrolment location (adjusted for study group)									
CHW	49	315	15.6	Ref.			Ref.		
PHC	238	285	83.5	92.82	18.92–455.42	<0.001	19.79	2.97–131.71	0.002
Study group by enrolment location									
CHW									
Pre-RAS	9	148	6	Ref.			Ref.		
Post-RAS									
No RAS use	16	76	21	3.14	1.03–9.60	0.04	3.97	1.07–14.75	0.04
RAS use	24	91	26	5.33	1.75–16.20	0.003	9.95	2.71–36.58	<0.001
PHC									
Pre-RAS	46	58	79	Ref.			Ref.		
Post-RAS									
No RAS use	102	107	95	13.00	3.11–54.42	<0.001	35.09	6.52–188.75	<0.001
RAS use	90	120	75	1.23	0.43–3.50	0.70	6.45	1.62–25.67	0.01

Enrolment location by LGA									
Mayo-Belwa - CHW	26	95	27.4	Ref.			Ref.		
Mayo-Belwa - PHC	134	156	85.9	16.62	3.50–78.93	<0.001	NA		
Fufore - CHW	5	145	3.4	0.04	0.01–0.25	<0.001	0.07	0.01–0.43	0.004
Fufore - PHC	79	100	79.0	32.81	5.27–204.46	<0.001	1.98	0.33–11.99	0.46
Song - CHW	18	75	24.0	0.62	0.15–2.58	0.51	0.50	0.12–2.07	0.34
Song - PHC	25	29	86.2	39.60	4.61–340.41	<0.001	3.20	0.33–30.93	0.32

* Danger signs involving the central nervous system (CNS): convulsions, unusually sleepy or unconscious
** Mai-October

Table S2 3. Estimated associations between child characteristics and referral completion, Uganda.

	Uganda								
	n	N	%	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
All	**2,170**	**3,745**	**57.9**						
Study group									
Pre-RAS	930	1,479	62.9	Ref.			Ref.		
Post-RAS									
No RAS use	365	635	57.5	0.79	0.63–1.00	0.05	0.80	0.63–1.01	0.06
RAS use	875	1,631	53.6	0.64	0.53–0.77	<0.001	0.72	0.58–0.88	0.002
Child gender									
Male	1,162	1,993	58.3	Ref.			Ref.		
Female	1,008	1,752	57.5	0.97	0.83–1.12	0.66	0.98	0.84–1.14	0.81
Age									
0	417	675	61.8	Ref.			Ref.		
1	637	1,078	59.1	0.92	0.74–1.15	0.48	0.93	0.74–1.17	0.54
2	500	890	56.2	0.74	0.59–0.93	0.01	0.74	0.58–0.94	0.01
3	401	694	57.8	0.84	0.65–1.07	0.15	0.83	0.65–1.07	0.16
4	215	408	52.7	0.69	0.52–0.92	0.01	0.69	0.51–0.92	0.01
Caregiver age									
<25	831	1,394	59.6	Ref.			Ref.		
25–34	868	1,484	58.5	0.92	0.78–1.09	0.36	0.93	0.78–1.11	0.44
35–44	327	608	53.8	0.82	0.66–1.03	0.08	0.84	0.66–1.06	0.13
>=45	143	258	55.4	0.87	0.64–1.18	0.37	0.91	0.66–1.25	0.55
Missing	1	1	100.0	NA			NA		
Caregiver gender									
Male	359	610	58.9	Ref.			Ref.		
Female	1,811	3,135	57.8	0.96	0.78–1.18	0.70	0.92	0.74–1.14	0.46
Health zone									
Ipamu	1,071	1,749	61.2	Ref.			Ref.		
Kenge	525	991	53.0	0.74	0.44–1.26	0.27	0.88	0.52–1.49	0.64
Kingandu	574	1,005	57.1	1.25	0.70–2.25	0.46	1.46	0.80–2.63	0.21
CNS involvement									
No	267	425	62.8	Ref.			Ref.		
Yes	1,903	3,320	57.3	0.67	0.53–0.86	0.002	0.80	0.61–1.04	0.09
Malaria test									
Negative / Not done	40	59	67.8	Ref.			Ref.		
Positive	2,130	3,686	57.8	0.81	0.43–1.49	0.49	0.90	0.48–1.67	0.74
Enrolment location									
CHW	2,170	3,745	57.9	NA			NA		
PHC	0	0	NA	NA			NA		
Enrolled during rainy season**									
No	772	1,392	55.5	Ref.			Ref.		
Yes	1,398	2,353	59.4	1.15	0.99–1.35	0.07	1.15	0.97–1.38	0.11

Enrolled on a workday									
No	516	959	53.8	Ref.			Ref.		
Yes	1,654	2,786	59.4	1.20	1.01–1.42	0.04	1.19	1.00–1.41	0.05
Enrolled during Covid-19 pandemic									
No	1,922	3,323	57.8	Ref.			Ref.		
Yes	248	422	58.8	0.87	0.68–1.11	0.25	0.90	0.69–1.19	0.48
Delay to enrolling provider									
0–1 days	1,212	2,134	56.8	Ref.			Ref.		
> 1 day	925	1,565	59.1	1.15	0.99–1.35	0.08	1.14	0.97–1.34	0.12
Missing	33	46	71.7	1.87	0.89–3.94	0.10	1.11	0.43–2.86	0.83
Transport to enrolling provider									
By foot / at home	2,002	3,462	57.8	Ref.			Ref.		
Vehicle	150	260	57.7	1.09	0.81–1.45	0.57	1.06	0.78–1.42	0.72
Missing	18	23	78.3	3.39	1.08–10.66	0.04	3.31	0.78–14.06	0.11
Time to RHF (min)									
0–<15	1,349	1,998	67.5	Ref.			Ref.		
15–<30	692	1,457	47.5	0.69	0.56–0.85	<0.001	0.72	0.58–0.89	0.003
30–<60	115	270	42.6	0.54	0.38–0.77	<0.001	0.55	0.39–0.79	0.001
> 60	0	2	0.0	NA			NA		
Missing	14	18	77.8	2.35	0.68–8.14	0.18	1.88	0.53–6.67	0.33
Perceived severity									
Not fatal	1,180	2,078	56.8	Ref.			Ref.		
Fatal	985	1,657	59.4	1.07	0.91–1.24	0.41	1.11	0.94–1.30	0.21
Missing	5	10	50.0	0.78	0.20–3.15	0.73	0.80	0.20–3.19	0.75
Home treatment									
No	1,876	3,271	57.4	Ref.			Ref.		
Yes	294	474	62.0	1.18	0.94–1.49	0.15	1.10	0.87–1.39	0.41
Missing	0	0	NA	NA			NA		

* Danger signs involving the central nervous system (CNS): convulsions, unusually sleepy or unconscious
** April-October

Supplement 3

Table S3 1. Estimated associations between child characteristics and referral timeliness, DRC.

				DRC					
	n	N	%	Undadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
All	**997**	**1,305**	**76.4**						
Study group									
Pre-RAS	154	223	69.1	Ref.			Ref.		
Post-RAS									
No RAS use	89	128	69.5	1.01	0.61–1.69	0.96	0.92	0.52–1.62	0.77
RAS use	754	954	79.0	1.49	1.04–2.14	0.03	1.39	0.92–2.12	0.12
Child gender									
Male	513	680	75.4	Ref.			Ref.		
Female	484	625	77.4	1.08	0.82–1.42	0.58	1.11	0.83–1.48	0.47
Age									
0	207	285	72.6	Ref.			Ref.		
1	323	413	78.2	1.46	1.00–2.13	0.05	1.56	1.06–2.31	0.02
2	214	283	75.6	1.29	0.86–1.95	0.21	1.26	0.83–1.92	0.28
3	140	173	80.9	1.71	1.03–2.82	0.04	1.48	0.88–2.49	0.14
4	113	151	74.8	1.09	0.66–1.82	0.73	1.07	0.63–1.81	0.80
Caregiver age									
<25	124	164	75.6	Ref.			Ref.		
25–34	377	500	75.4	0.96	0.62–1.50	0.87	0.85	0.53–1.35	0.49
35–44	357	458	77.9	1.01	0.64–1.61	0.95	0.85	0.52–1.40	0.53
>=45	139	183	76.0	0.83	0.48–1.41	0.48	0.76	0.42–1.34	0.34
Not documented	0	0	NA	NA			NA		
Caregiver gender									
Male	557	716	77.8	Ref.			Ref.		
Female	440	589	74.7	0.86	0.63–1.16	0.31	0.78	0.56–1.09	0.15
Health zone									
Ipamu	418	514	81.3	Ref.			Ref.		
Kenge	345	485	71.1	0.53	0.29–0.97	0.04	0.54	0.29–1.02	0.06
Kingandu	234	306	76.5	0.72	0.38–1.34	0.29	0.75	0.38–1.49	0.41
CNS involvement*									
No	358	493	72.6	Ref.			Ref.		
Yes	639	812	78.7	1.55	1.16–2.07	0.003	1.50	1.10–2.04	0.01
Malaria test									
Negative / Not done	38	47	80.9	Ref.			Ref.		
Positive	959	1,258	76.2	0.71	0.31–1.63	0.41	0.39	0.13–1.21	0.10
Enrolment location									
CHW	31	38	81.6	Ref.			Ref.		
PHC	966	1,267	76.2	0.65	0.22–1.92	0.43	0.63	0.21–1.86	0.40

Enrolled during rainy season**									
No	501	627	79.9	Ref.			Ref.		
Yes	496	678	73.2	0.71	0.54–0.95	0.02	0.73	0.53–1.01	0.06
Enrolled on a workday									
No	267	341	78.3	Ref.			Ref.		
Yes	730	964	75.7	0.83	0.61–1.15	0.26	0.83	0.59–1.15	0.25
Enrolled during Covid-19 pandemic									
No	764	1,005	76.0	Ref.			Ref.		
Yes	233	300	77.7	1.09	0.77–1.54	0.62	0.83	0.57–1.22	0.35
Delay to enrolling provider									
0–1 days	296	396	74.7	Ref.			Ref.		
> 1 day	671	873	76.9	1.19	0.87–1.61	0.27	1.69	1.20–2.38	0.003
Not documented	30	36	83.3	1.43	0.51–4.01	0.50	2.29	0.35–14.86	0.38
Transport to enrolling provider									
By foot / at home	786	1,024	76.8	Ref.			Ref.		
Vehicle	181	243	74.5	0.82	0.56–1.21	0.33	0.88	0.59–1.31	0.53
Not documented	30	38	78.9	0.93	0.37–2.34	0.88	0.37	0.07–1.97	0.25
Time to RHF (min)									
0–<15	498	636	78.3	Ref.			Ref.		
15–<30	157	213	73.7	0.95	0.59–1.53	0.84	0.98	0.59–1.61	0.92
30–<60	147	202	72.8	0.83	0.51–1.35	0.46	0.82	0.49–1.38	0.46
≥60	44	69	63.8	0.60	0.31–1.16	0.13	0.58	0.28–1.18	0.13
Missing	151	185	81.6	1.32	0.80–2.17	0.28	1.25	0.72–2.15	0.43
Perceived severity									
Not fatal	690	907	76.1	Ref.			Ref.		
Fatal	294	384	76.6	0.91	0.67–1.26	0.59	0.92	0.66–1.28	0.61
Not documented	13	14	92.9	1.63	0.18–14.28	0.66	1.73	0.19–15.97	0.63
Home treatment									
No	339	406	83.5	Ref.			Ref.		
Yes	658	899	73.2	0.53	0.38–0.75	<0.001	0.49	0.33–0.71	<0.001
Not documented	0	0	NA	NA			NA		

* Danger sign involving the central nervous system (CNS): convulsions, unusually sleepy or unconscious
** October-April

Table S3 2. Estimated associations between child characteristics and referral timeliness, Nigeria.

	Nigeria								
	n	N	%	Undadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
All	**204**	**238**	**85.7**						
Study group									
Pre-RAS	29	35	82.9	Ref.			Ref.		
Post-RAS									
No RAS use	84	101	83.2	1.02	0.37–2.84	0.97	1.33	0.36–4.85	0.67
RAS use	91	102	89.2	1.71	0.58–5.04	0.33	1.53	0.36–6.40	0.56
Child gender									
Male	114	140	81.4	Ref.			Ref.		
Female	90	98	91.8	2.57	1.11–5.94	0.03	2.73	1.03–7.28	0.04
Age									
0	21	24	87.5	Ref.			Ref.		
1	58	70	82.9	0.69	0.18–2.69	0.59	0.48	0.09–2.67	0.40
2	64	73	87.7	1.02	0.25–4.11	0.98	0.68	0.13–3.65	0.65
3	35	39	89.7	1.25	0.25–6.14	0.78	0.83	0.12–5.87	0.86
4	26	32	81.3	0.62	0.14–2.78	0.53	0.54	0.08–3.54	0.52
Caregiver age									
<25	42	48	87.5	Ref.			Ref.		
25–34	98	117	83.8	0.74	0.27–1.98	0.54	0.40	0.12–1.35	0.14
35–44	48	54	88.9	1.14	0.34–3.81	0.83	0.49	0.11–2.12	0.34
>=45	16	19	84.2	0.76	0.17–3.42	0.72	0.25	0.04–1.69	0.15
Not documented	0	0	NA	NA			NA		
Caregiver gender									
Male	63	69	91.3	Ref.			Ref.		
Female	141	169	83.4	0.48	0.19–1.22	0.12	0.42	0.12–1.41	0.16
LGA									
Mayo-Belwa	112	135	83.0	Ref.			Ref.		
Fufore	56	65	86.2	1.31	0.48–3.56	0.60	0.84	0.30–2.40	0.75
Song	36	38	94.7	3.78	0.78–18.32	0.10	5.42	1.02–28.68	0.05
CNS involvement									
No	18	26	69.2	Ref.			Ref.		
Yes	186	212	87.7	3.18	1.26–8.05	0.01	4.78	1.28–17.77	0.02
Malaria test									
Negative / Not done	9	10	90.0	Ref.			Ref.		
Positive	195	228	85.5	0.66	0.08–5.35	0.69	1.58	0.15–16.73	0.71
Enrolment location									
CHW	30	39	76.9	Ref.			Ref.		
PHC	174	199	87.4	2.09	0.89–4.91	0.09	1.73	0.45–6.60	0.42
Enrolled during rainy season**									
No	56	66	84.8	Ref.			Ref.		
Yes	148	172	86.0	1.10	0.50–2.45	0.81	0.59	0.20–1.74	0.34

Enrolled on a workday									
No	24	27	88.9	Ref.			Ref.		
Yes	180	211	85.3	0.73	0.21–2.56	0.62	0.78	0.18–3.41	0.74
Enrolled during Covid-19 pandemic									
No	165	195	84.6	Ref.			Ref.		
Yes	39	43	90.7	1.77	0.59–5.33	0.31	1.90	0.49–7.44	0.35
Delay to enrolling provider									
0–1 days	77	89	86.5	Ref.			Ref.		
> 1 day	122	144	84.7	0.86	0.40–1.85	0.71	0.63	0.25–1.58	0.33
Not documented	5	5	100.0	NA			NA		
Transport to enrolling provider									
No vehicle	70	84	83.3	Ref.			Ref.		
Vehicle	134	154	87.0	1.44	0.69–3.04	0.33	1.14	0.40–3.24	0.81
Not documented	5	5	100.0	NA			NA		
Time to RHF (min)									
0–<15	62	70	88.6	Ref.			Ref.		
15–<30	46	48	95.8	2.97	0.60–14.64	0.18	1.72	0.31–9.69	0.54
30–<60	59	75	78.7	0.48	0.19–1.19	0.11	0.38	0.14–1.06	0.07
> 60	34	41	82.9	0.63	0.21–1.88	0.40	0.75	0.20–2.83	0.67
Missing	3	4	75.0	0.39	0.04–4.18	0.43	0.16	0.01–2.76	0.21
Perceived severity									
Not fatal	155	180	86.1	Ref.			Ref.		
Fatal	49	58	84.5	0.88	0.38–2.01	0.76	0.93	0.34–2.52	0.88
Not documented	0	0	NA	NA			NA		
Home treatment									
No	117	138	84.8	Ref.			Ref.		
Yes	87	100	87.0	1.20	0.57–2.53	0.63	1.02	0.42–2.49	0.96
Not documented	0	0	NA	NA			NA		

* Danger sign involving the central nervous system (CNS): convulsions, unusually sleepy or unconscious
** Mai-October

Table S3 3. Estimated associations between child characteristics and referral timeliness, Uganda.

	Uganda								
	n	N	%	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
All	**1,880**	**2,055**	**91.5**						
Study group									
Pre-RAS	780	873	89.3	Ref.			Ref.		
Post-RAS									
No RAS use	321	350	91.7	1.40	0.88–2.20	0.15	1.43	0.89–2.30	0.14
RAS use	779	832	93.6	1.91	1.31–2.79	<0.001	1.81	1.17–2.79	0.01
Child gender									
Male	1,003	1,105	90.8	Ref.			Ref.		
Female	877	950	92.3	1.23	0.89–1.69	0.21	1.23	0.89–1.71	0.21
Age									
0	358	395	90.6	Ref.			Ref.		
1	559	611	91.5	1.15	0.73–1.80	0.55	1.15	0.73–1.83	0.54
2	438	470	93.2	1.44	0.87–2.39	0.15	1.49	0.89–2.49	0.13
3	345	382	90.3	0.97	0.59–1.58	0.89	0.89	0.53–1.47	0.64
4	180	197	91.4	1.14	0.62–2.11	0.68	1.01	0.53–1.90	0.99
Caregiver age									
<25	713	791	90.1	Ref.			Ref.		
25–34	752	818	91.9	1.25	0.88–1.77	0.22	1.33	0.92–1.91	0.13
35–44	289	309	93.5	1.60	0.95–2.69	0.08	1.81	1.04–3.13	0.03
>=45	125	136	91.9	1.22	0.62–2.39	0.56	1.22	0.60–2.49	0.59
Not documented	1	1	100.0	NA			NA		
Caregiver gender									
Male	312	341	91.5	Ref.			Ref.		
Female	1,568	1,714	91.5	1.03	0.67–1.58	0.89	1.21	0.77–1.92	0.41
Health zone									
Ipamu	928	1,017	91.2	Ref.			Ref.		
Kenge	451	507	89.0	0.86	0.55–1.34	0.49	0.65	0.41–1.03	0.07
Kingandu	501	531	94.4	1.74	1.04–2.92	0.03	1.19	0.67–2.12	0.56
CNS involvement									
No	223	246	90.7	Ref.			Ref.		
Yes	1,657	1,809	91.6	1.21	0.74–1.96	0.45	1.13	0.66–1.92	0.65
Malaria test									
Negative / Not done	35	39	89.7	Ref.			Ref.		
Positive	1,845	2,016	91.5	1.18	0.40–3.44	0.77	0.94	0.31–2.81	0.91
Enrolment location									
CHW	1,880	2,055	91.5	NA			NA		
PHC	0	0	NA	NA			NA		
Enrolled during rainy season**									
No	680	738	92.1	Ref.			Ref.		
Yes	1,200	1,317	91.1	0.92	0.65–1.28	0.61	0.97	0.67–1.40	0.87

Enrolled on a workday									
No	439	480	91.5	Ref.			Ref.		
Yes	1,441	1,575	91.5	0.99	0.68–1.44	0.97	1.06	0.72–1.54	0.78
Enrolled during Covid-19 pandemic									
No	1,659	1,817	91.3	Ref.			Ref.		
Yes	221	238	92.9	1.27	0.74–2.17	0.39	0.97	0.53–1.78	0.93
Delay to enrolling provider									
0–1 days	1,119	1,189	94.1	Ref.			Ref.		
> 1 day	755	860	87.8	0.45	0.33–0.62	<0.001	0.48	0.34–0.68	<0.001
Not documented	6	6	100.0	NA			NA		
Transport to enrolling provider									
By foot / at home	1,745	1,912	91.3	Ref.			Ref.		
Vehicle	135	143	94.4	1.56	0.74–3.26	0.24	1.70	0.80–3.60	0.17
Not documented	0	0	NA	NA			NA		
Time to RHF (min)									
0–<15	1,168	1,277	91.5	Ref.			Ref.		
15–<30	605	657	92.1	1.21	0.82–1.81	0.34	1.10	0.75–1.63	0.61
30–<60	94	107	87.9	0.77	0.39–1.53	0.46	0.61	0.30–1.24	0.17
> 60	0	0	NA	NA			NA		
Missing	13	14	92.9	1.30	0.16–10.55	0.81	1.25	0.14–10.82	0.84
Perceived severity									
Not fatal	1,017	1,109	91.7	Ref.			Ref.		
Fatal	859	942	91.2	0.96	0.70–1.33	0.82	0.94	0.67–1.31	0.70
Not documented	4	4	100.0	NA			NA		
Home treatment									
No	1,635	1,774	92.2	Ref.			Ref.		
Yes	245	281	87.2	0.59	0.40–0.89	0.01	0.69	0.45–1.04	0.08
Not documented	0	0	NA	NA			NA		

* Danger sign involving the central nervous system (CNS): convulsions, unusually sleepy or unconscious
** April-October