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Three-dose completion of R21/matrix-M malaria vaccine among children eligible for the third dose in Kole and Kwania districts, Uganda: a parallel mixed-methods study

Sean Steven Puleh[1,2] · Moses Ocan[3] · Godfrey Siu[4] · Adoke Yeka[5,6] · Joaniter I. Nankabirwa[1,5] · Richard Idro[7] · Stella Immaculate Akech[1,2] · Joy Acen[1] · David L. Ejalu[1] · Ziadah Nankinga[1] · Robert Afayo[1] · Joan N. Kalyango[1,8]

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Abstract

Background The R21/Matrix-M malaria vaccine (hereafter "R21") contains the R21 antigen and Matrix-M adjuvant. Completion of the initial three-dose series is important for protection, but continuation through multi-dose schedules remains a programme challenge. This study assessed three-dose completion and associated factors among children who had initiated vaccination and were eligible for dose three in Kole and Kwania districts, Uganda, and explored barriers and facilitators of completion.

Methods A convergent mixed-methods was conducted from September to October 2025. A community-based cross-sectional survey included caregivers of 733 children who had received dose one at least 3 months before enrolment. Descriptive analyses and modified Poisson regression with village-clustered robust standard errors were used; adjusted prevalence ratios (aPRs) and 95% confidence intervals were reported. Qualitative data were collected from 55 participants through key informant interviews, caregiver in-depth interviews and caregiver focus group discussions using semi-structured guides. Recordings were transcribed, anonymised and analysed in ATLAS.ti 25. The components were analysed separately and integrated through a convergence matrix.

Results Of the 733 children, 399 (54.4%) were female and 404 (55.1%) were aged ≤12 months. Three-dose completion was 55.7% (village-clustered 95% CI: 48.6–62.7). Among the 408 children who completed three doses, 360 (88.2%) received the third dose within the specified timing window. In the adjusted analysis of 727 children, caregiver-reported vaccine unavailability was associated with lower completion (aPR 0.64, 95% CI: 0.44–0.93). Health-worker reminders were not significantly associated with completion (aPR 1.09), and walking time was not statistically significant overall ($p = 0.074$). Qualitative analysis involving 55 participants identified two overarching themes: factors supporting completion, including perceived benefits, caregiver motivation, reminders, and community support; and barriers, including missed appointments, vaccine unavailability, transport difficulties, safety concerns, and gender-related responsibilities.

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Conclusions Just over half of children completed the initial three-dose R21/Matrix-M series. Caregiver-reported vaccine unavailability was associated with lower completion, while qualitative findings highlighted practical barriers and sources of support. The Ministry of Health should prioritise reliable vaccine availability and evaluate outreach and reminder strategies to support completion.

Keywords Childhood vaccination · Adherence · Primary doses · Caregivers · Health systems · Uganda

Abbreviations

AEFI	Adverse Events Following Immunisation
aPR	Adjusted Prevalence Ratio
CI	Confidence intervals
cPR	Crude Prevalence Ratio
FGD	Focus group discussion
IDI	In-depth interviews
HBM	Health Belief Model
KII	Key informant interviews
LC	Local Council
RTS,S	RTS,S/AS01 malaria vaccine
SRS	Simple Random Sampling
SD	Standard Deviation
VHT	Village health team

Background

Globally there were an estimated 282 million new malaria cases that occurred across 80 endemic countries in 2024, representing an increase from 273 million cases in the previous year [1]. Sub-Saharan Africa (SSA) had the highest malaria burden accounting for approximately 94% of all cases and 95% of the deaths globally [1]. Uganda accounted for 5% of the global malaria cases, making it the third-highest burden country worldwide after Nigeria (25.9%) and the Democratic Republic of the Congo (12.6%) [1]. The increased burden has been attributed to development of insecticide and drug resistance [2, 3], underscoring the limits of relying solely on existing control measures.

To strengthen prevention, the World Health Organization (WHO) recommended malaria vaccines as an additional tool alongside the existing interventions [4–6]. In endemic settings, the malaria vaccines like RTS,S/AS01 and R21/Matrix-M have demonstrated substantial impact in reducing clinical and severe malaria in children under 5 years of age [7, 8]. The phase 3 trials of the R21/Matrix-M vaccine demonstrated 12-month efficacy of 75% against clinical malaria episodes in young children in settings with seasonal malaria and 68% at standard perennial-transmission sites [8–11]. Uganda's Ministry of Health adopted the R21/Matrix-M malaria vaccine and this is integrated into the routine immunization programmes to reduce malaria related-illness and death in young children [5]. Uganda nationally launched malaria vaccination on 2 April 2025 [12]. Kole and Kwania were included in the early rollout. These districts are relevant for malaria vaccine research because they combine high epidemiological relevance with practical programmatic strengths such as strong network of health facilities and village health teams.

Vaccine efficacy alone did not ensure completion of a multi-dose schedule. RTS,S implementation in Ghana, Kenya and Malawi demonstrated challenges in maintaining attendance across successive doses [13–15]. R21/Matrix-M implementation in Uganda similarly required continued attendance beyond initiation. Local rollout included radio messages and Village Health Team mobilisation [16], providing a context in which continuation needed assessment rather than a basis for assuming better adherence. This study aimed to assess adherence to the

first three-dose schedule of the malaria vaccine and associated factors among children eligible for the third dose in Kole and Kwania districts, Uganda, and to explore the promoters and barriers of adherence through qualitative interviews and discussions with caregivers, health workers, and community leaders.

Methods

Study design and setting

This study employed a parallel convergent mixed methods design [17]. A community-based cross-sectional survey assessed three-dose completion and associated factors, while concurrent qualitative interviews and focus group discussions explored caregivers', healthcare workers', and community leaders' experiences of vaccination. The components were conducted in parallel and analysed separately before integration. We adopted a hybrid inductive-deductive approach by developing initial codes from participants' accounts, and the resulting themes were subsequently interpreted using the Health Belief Model. Findings were integrated through a convergence matrix to identify agreement, complementary insights, and discrepancies between the components.

The study was conducted between September and October 2025 in Kole and Kwania districts, northern Uganda. Northern Uganda is a high transmission region and based on the 2024–2025 Malaria Indicator Survey, the malaria prevalence among children aged 5–59 months in Lango sub-region, was 32%, the highest in Uganda [18]. The two districts have Malaria Reference Centers (MRCs) which act as malaria sentinel sites. Kole district has 6 sub-counties, 4 town councils, 41 parishes and 692 villages [19], while Kwania district has two counties, eight sub-counties, three town councils, 49 parishes/wards and 447 villages/cells [20]. Before the introduction of the malaria vaccine, malaria control in both Kole and Kwania districts has largely been limited to the use of long-lasting insecticidal nets, and treatment of cases with artemisinin-based combination therapies. To encourage adherence to the dose schedule, vaccine roll-out included radio talk shows and active participation of Village Health Teams, who shared information and encouraged caregivers to take the eligible children for the subsequent doses as described previously [16].

Study population and eligibility criteria for the quantitative survey

Children were eligible to participate only if: (1) they had received the first dose of the malaria vaccine at least 3 months earlier, (2) had a caregiver who provided written informed consent, (3) had resided in the study catchment area for at least 6 months, at the time of enrolment. Children were excluded if (1) they had caregivers who did not speak Luo or English.

Sample size determination

The sample size was computed using the formula for single proportions with adjustment for clustering [21]. Based on that formula, the parameters used were 95% confidence level, 5% sampling error, design effect of 2, and an estimated third-dose malaria vaccine uptake of 69.5%, as reported by Simbeye et al. (2024) in Malawi [22]. The reference estimate included vaccination records and caregiver recall and was used as an approximation for documented completion in the present study. The number of participants per cluster was estimated from WHO methods for cluster survey [23]. A minimum recruitment target of 724 caregiver–child pairs was obtained after dividing the cluster-adjusted requirement by 0.90 to accommodate 10% non-response. A total of 733 caregiver–child pairs were enrolled across 30 villages.

Procedures for sampling, and household enrolment in the quantitative survey

A multistage cluster sampling design was used to select study participants. A cluster was defined as a village in Kole or Kwania districts. First, two districts Kwania and Kole were purposively selected based on the presence of the MRCs. Within each district, two sub-counties were selected using simple random sampling (SRS) followed by three parishes per selected sub-county and two villages per selected parish, yielding 24 initially selected villages. Where a village did not provide enough eligible participants to meet the recruitment target, recruitment extended to a neighbouring village. Six additional villages were included through this process, bringing the total to 30 villages. Village-level recruitment by district is presented in Supplementary File 1 *(Supplementary File 1)*. Household lists were compiled with support from community health workers and local council leaders. Recruitment across the 30 villages ranged from 15 to 33 caregiver–child pairs, with a mean of 24.4 per village. Achieved recruitment by district and village, including identification of the 24 initially selected and six additional villages. The sampling interval was calculated by dividing the number of listed households by the recruitment target. Following a random starting point, every kth household was approached. A random starting point between 1 and k was chosen, and thereafter every kth household was selected. If a selected household did not have an eligible child, the next household on the list was approached. If a selected household had no eligible child, the next listed household was approached. In households with multiple eligible children, one child was selected by simple random sampling. Fixed village recruitment targets, neighbouring-village additions and household substitution did not establish equal selection probabilities. The sampling procedure may have introduced unequal selection probabilities and selection bias, limiting population representativeness. Village-clustered standard errors accounted for within-village dependence but did not correct these limitations.

Study variables

Sociodemographic characteristics included caregiver variables such as age, sex, relationship to the child, education level, occupation, religion, and household size. Child variables included sex and age.

Three-dose completion was defined as recorded (documented) receipt of the first three malaria vaccine doses in sequence by the survey date, irrespective of age at administration. The estimate applied to sampled vaccine initiators who had received dose one at least 3 months earlier; it did not represent vaccination coverage among all age-eligible children. Non-completion at the survey did not establish permanent discontinuation.

Timeliness was assessed separately from completion using a study-defined window of ±4 weeks around the scheduled ages for doses two and three [24]. Second-dose timeliness was estimated among second-dose recipients with available timing information; third-dose timeliness was estimated among three-dose recipients with available timing information.

Routine immunization status was measured by determining whether children were fully immunized according to the national immunization schedule or only partially immunized.

Health system factors included caregiver-reported vaccine unavailability and receipt of health-worker reminders. Reports of unavailability were not treated as independently verified facility stock-outs. Transport difficulties and schedule constraints were described separately from these measures.

Caregiver-related variables included concerns about vaccine safety, cultural or religious discouragement, forgetting vaccination appointments, discouragement from returning for vaccination, and experiences of adverse events following vaccination.

Child-related variables included malaria episodes following vaccination, complications after vaccination, and receipt of other routine vaccines.

Routine immunization status was collected as a contextual indicator of vaccination service utilization but was not included in the adherence model because it was not a primary explanatory variable.

Accessibility was measured by walking time to the nearest health facility and reported difficulty accessing healthcare services.

Data collection for the quantitative study

Caregivers who were eligible to participate were provided with comprehensive information about the study purpose. After obtaining written informed consent, data were collected electronically by five research assistants using the KoBoCollect® application on the KoBoToolbox platform (http://www.kobotoolbox.org/). Confidentiality was maintained in this study by assigning unique study codes instead of names, and no personally identifiable information was included in the datasets. Before data collection, assistants underwent training on the study objectives, ethical principles, and standardized interviewing techniques to ensure consistency and reliability.

The questionnaire was informed by the Health Belief Model, covering perceived susceptibility, severity, benefits, barriers, cues to action and self-efficacy. Experts reviewed its content, and it was pretested in Dokolo District for clarity and cultural relevance. A Cronbach's alpha of 0.72 was reported for the pretest; this indicated internal consistency only for the item set assessed and did not establish validity of the entire questionnaire..

The questionnaire *(Supplementary 2)* collected information on caregiver and child characteristics, vaccination history, adherence to the first three-dose schedule R21 malaria vaccine and factors influencing adherence. Where available, vaccination cards were reviewed to confirm reported doses and dates to improve accuracy. Quantitative data included sociodemographic characteristics, completion of the first three doses, health system factors, cultural and social factors, issues in program implementation, and prior health experiences with vaccination.

Quantitative data management and analysis

Data were cleaned and exported to Stata version 18. Participant characteristics and vaccination outcomes were summarised using unweighted counts and percentages. Three-dose completion was assessed by the survey date, and its proportion and 95% confidence interval were estimated using village-clustered robust standard errors. Timeliness was described separately among dose recipients with available timing information; missing timing information was not classified as untimely vaccination.

Factors associated with completion were examined using modified Poisson regression with a log link. Robust standard errors were clustered across 30 villages to account for within-village correlation, with independence assumed between villages. Model estimates were reported as crude prevalence ratios (cPRs) and adjusted prevalence ratios (aPRs), with 95% confidence intervals. Regression confidence intervals used the normal approximation, category-specific p-values were obtained from z tests, and overall categorical associations were assessed using cluster-robust joint Wald tests.

Covariates were selected based on substantive relevance and measurement characteristics. The final adjusted model included child age and sex, caregiver age and sex, education, occupation, walking time, caregiver-reported vaccine unavailability and health-worker reminders. It estimated 16 coefficients, including the intercept. Retrospective reasons for missed doses and caregiver-reported malaria after vaccination were excluded because their ascertainment or temporal relationship with completion was uncertain. Crude models included each characteristic separately, while the adjusted model included all nine characteristics simultaneously. Both analyses used the same complete-case sample of 727 children. Six children with missing vaccine-unavailability responses were excluded, and missing responses were not coded as absence of exposure.

Background and expanded models were fitted to the same complete-case sample to examine changes following additional adjustment. Exploratory sensitivity analyses assessed estimate stability by removing each covariate individually and comparing the remaining category-specific prevalence ratios with those from a reference model that included child age but not child sex. Absolute percentage changes were calculated relative to the reference-model prevalence ratios. These analyses used village-clustered robust standard errors and assessed estimate stability without determining which covariates were retained.

Model comparison and sensitivity analyses

Background and expanded models were fitted to the same complete-case sample to examine changes following additional adjustment. Overall associations for categorical variables were assessed using cluster-robust joint Wald tests. An exploratory interaction between walking time and caregiver-reported vaccine unavailability was assessed using a joint Wald test.

Exploratory leave-one-covariate-out analyses assessed estimate stability by removing each covariate individually and comparing remaining category-specific prevalence ratios with those from the reference model. Absolute percentage changes were calculated relative to reference-model prevalence ratios. The sensitivity reference model included child age but not child sex; all models used the same 727 participants. These comparisons informed sensitivity assessment rather than automatic covariate selection. Cluster-robust Wald tests, rather than likelihood-ratio tests or conventional Poisson AIC/BIC, informed hypothesis assessment.

Study population and eligibility for the qualitative component

The study population consisted of caregivers of children who had received malaria vaccinations. They were recruited to participate in in-depth interviews and focus group discussions. Furthermore, healthcare providers (nurses, midwives, clinical officers), Village Health Teams (VHTs), and community leaders who were actively engaged in malaria vaccination activities were purposively selected as key informants. Eligibility criteria required participants to be adults aged 18 years or older and able to communicate competently in Luo or English. In order to ensure a conducive environment for open dialogue, interviews and discussions were conducted in private settings, with participants encouraged to freely express their views without fear of reprisal. This approach enhanced the richness of the data by fostering trust and minimizing social desirability bias.

Qualitative data collection methods, tools and sampling procedure

A total of 55 qualitative participants were purposively selected, including 41 caregivers in four focus group discussions, five caregivers in five in-depth interviews, and nine key informants. Of the 55 qualitative participants, 28 were drawn from Kole District and 27 from Kwania District, ensuring balanced representation across the two study sites. Participants for the FGDs and IDIs were selected using maximum variation sampling based on age, gender, educational status, occupation, and experience of adverse events. Community leaders and healthcare workers were used to identify the study participants. Qualitative data were collected through KIIs, IDIs, and FGDs using their respective semi-structured interview guides *(Supplementary 3)*. Saturation was assessed iteratively during data collection and analysis. After each interview and focus group, transcripts were coded and emerging themes reviewed. Thematic saturation was considered reached when no new codes or themes emerged in three consecutive interviews, and subsequent data only confirmed existing categories.

A pretest was conducted with two eligible participants in Dokolo district to evaluate the quality of the recording, to further improve the interview guide. Pretest feedback resulted in slight adjustments to question wording for clarity, reordering of items for flow, and modifications to probes for more detailed responses. These participants were excluded from the final analysis. Interviews were conducted by six trained research assistants with backgrounds in Social Sciences and Public Health who had additional training in interviewing, active listening, and rapport building. None of the assistants was involved in vaccine administration, which helped maintain independence and reduce power imbalances. Although IDIs, KIIs, and FGDs followed the same ethical procedures informed consent, assurances of confidentiality, audio-recording, and use of private venues, they differed in format and purpose. IDIs and KIIs were conducted as one-on-one conversations, each lasting about 45 min, allowing participants to share personal experiences or professional insights in depth. FGDs, on the other hand, brought groups together for collective discussion and interaction, and therefore ran longer, averaging about 1 h and 20 min.

Qualitative data management and analysis

All interviews and group discussions were transcribed verbatim and, where necessary, translated before being analyzed thematically in ATLAS.ti version 25. Each transcript was checked against audio recordings and field notes to ensure accuracy. Translations into English were carried out by a bilingual social scientist, and to preserve nuance, 20% of transcripts were back-translated by an independent bilingual speaker. Any discrepancies were resolved through team consensus. Coding unfolded in three stages: open coding (line-by-line inductive codes), axial coding (grouping related codes and exploring connections), and selective coding (refining core themes and aligning them with the Health Belief Model). The codebook was refined iteratively through team discussions, with majority decisions documented in the audit trail.

Reflexivity was central to our process. The six interviewers three male; OD. OE and OG, three female, AP, AC, and AE all with a background in Public Health or Social Sciences brought disciplinary perspectives that naturally emphasized health system and behavioural dimensions. We recognize this may have limited exploration of cultural or emotional aspects of caregiver decision-making. To address this, the team held reflexive discussions throughout analysis, critically examining how positionality influenced coding and interpretation. Trustworthiness was strengthened through triangulation across methods and respondent groups, coding discussions, a detailed audit trail, reflexivity, and translation checks. Maximum variation sampling further enhanced transferability. Importantly, no non-participants were present during interviews or FGDs, ensuring participants could speak freely. Additionally, transcripts were not returned to the participants for validation.

Results

Participant recruitment and vaccination status

Of the 742 children screened, nine were excluded: six because their caregivers could not participate in the available study languages (Luo or English), and three because their caregivers declined participation. No child was excluded because of a history of severe adverse events following vaccination. A total of 733 children were enrolled (Fig. 1), comprising 370 (50.5%) from Kole District and 363 (49.5%) from Kwania District. Vaccination-card verification established that 408 children had completed three doses, corresponding to a completion prevalence of 55.7% (95% CI 48.6–62.7). The confidence interval accounted for clustering within 30 villages. At the time of the survey, 172 children (23.5%) had a record of exactly two doses and 153 (20.9%) had a record of only one dose (Table 1).

Participant recruitment and sociodemographic characteristics of caregivers and children

Among 733 enrolled children, 54.4% were female, and 55.1% were aged ≤12 months. Most caregivers were young women (58.7% aged ≤25 years; 94.5% female), biological mothers (94.1%), and subsistence farmers (83.8%) (Table 2).

R21 malaria vaccination adherence, timeliness and routine vaccination status

Of the 733 children enrolled, adherence to the first three-dose schedule was 55.7% (95% CI: 48.6–62.7). The confidence interval accounted for clustering within 30 villages. Among 580 s-dose recipients, timing information was available for 453 children. Of these, 402 (88.7%) received the second dose within the specified window. Timing information was unavailable for 127 recipients (21.9%) (Table 3).

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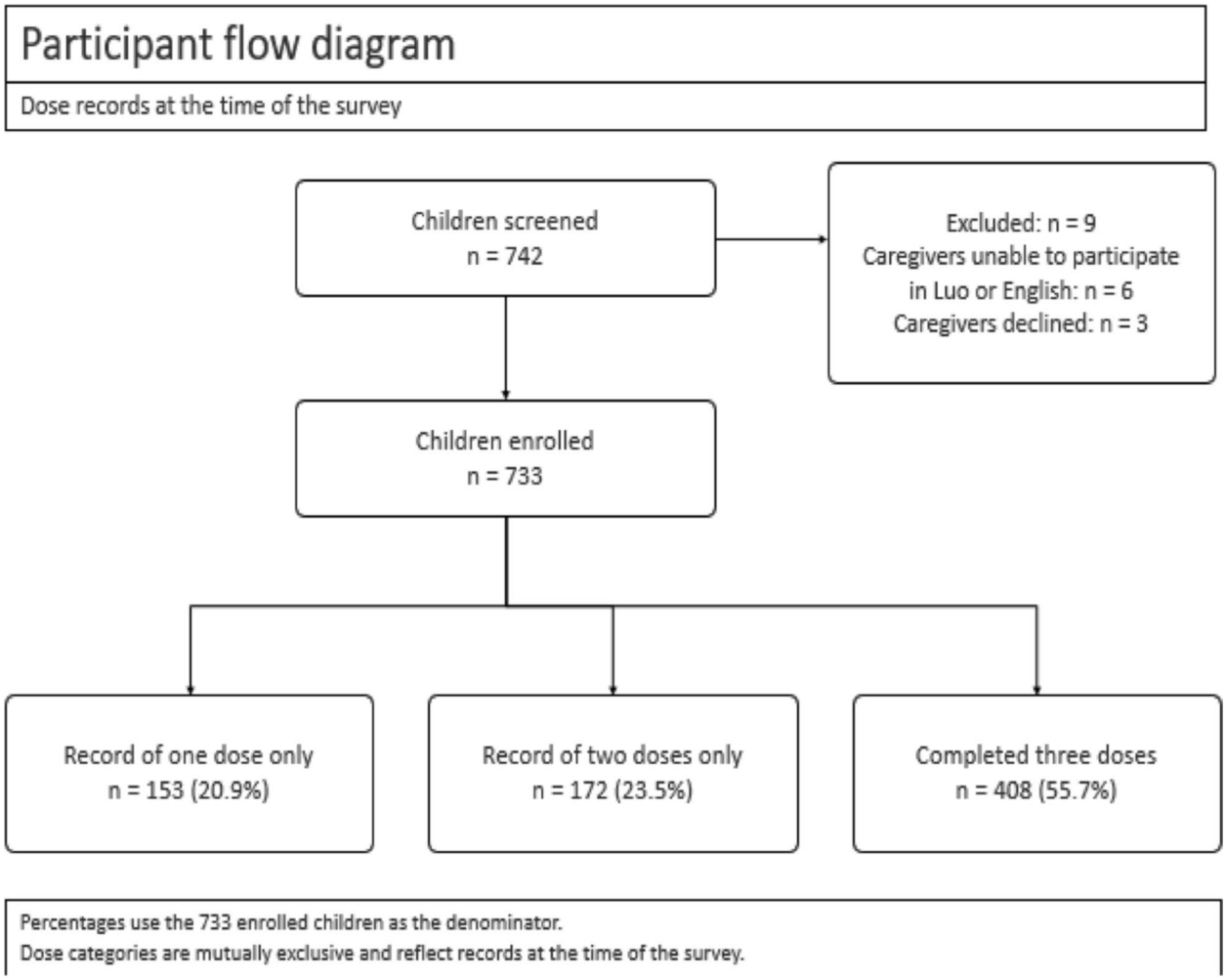


Fig. 1 Participant flow diagram

Table 1 Recruitment, district of residence, and recorded vaccination status

Characteristic	Number	Percentage
Children screened	742	–
Children excluded	9	–
Caregiver unable to participate in Luo or English	6	–
Caregiver declined participation	3	–
Children enrolled	733	100.0
District of residence		
Kole	370	50.5
Kwania	363	49.5
Recorded vaccination status at the survey		
One dose only	153	20.9
Exactly two doses	172	23.5
Three doses completed	408	55.7

Percentages for district and vaccination status use the 733 enrolled children as the denominator. Dose categories are mutually exclusive. The village-clustered 95% confidence interval for three-dose completion was 48.6–62.7%

Table 2 Sociodemographic characteristics of caregivers and children (N = 733)

Characteristic	Category	Frequency (n)	Percent (%)
Child sex	Female	399	54.4
	Male	334	45.6
Child's age categories (months)	Infants (≤ 12 months)	404	55.1
	Toddlers (> 1 year)	329	44.9
Caregiver age (years)	≤25	430	58.7
	26–35	249	34.0
	≥36	54	7.4
Caregiver sex	Female	693	94.5
	Male	40	5.5
Relationship to child	Biological mother	690	94.1
	Biological father	30	4.1
	Other (grandparent/aunt)	13	1.8
Education level of the caregiver	None	33	4.5
	Primary	562	76.7
	Secondary	117	16.0
	Tertiary	21	2.9
Occupation of the caregiver	Peasant farmer	614	83.8
	Business	58	7.9
	Civil servant	15	2.1
	Other	46	6.3
Religion	Anglican	297	40.5
	Catholic	338	46.1
	Pentecostal	76	10.4
	Other	22	3.0
Household size	≤4	405	55.3
	>4	328	44.7

Table 3 R21 malaria vaccine adherence, timeliness and routine vaccination status

Indicator	Category	Frequency	Percentage	95 percent CI
Number of R21 doses received by the survey date	One dose only	153	20.9	–
	Two doses only	172	23.5	–
	Dose three	408	55.7	–
Adherence to third dose	Adhered	408	55.7	48.6–62.7
	Non-adherent	325	44.3	37.4–51.5
Timeliness of second dose	Timely	402(453)	88.7	82.5–95.0
Timeliness of third dose	Timely	360	88.2	84.7–91.0
Routine immunisation status	Fully immunised	300	40.9	–

Second-dose timeliness used 453 recipients with available timing information; 127 of 580 s-dose recipients lacked timing information. Third-dose timeliness used 408 recipients. Missing timing information was not classified as untimely

Reported reasons for non-adherence to the first three-dose schedule of the malaria vaccine doses among children who received up to the second dose only (N = 172)

Among the 172 children who received the second but missed the third dose, the most frequently reported reason (34.9%) of the caregivers reported forgetting the vaccination date as the reason for the missed dose. Vaccine stock-outs were reported by 28.5% of the caregivers, followed by lack of transport to the health facility 15.7%.

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Table 4 Reasons for non-adherence to the third malaria vaccine dose among children who received only the second dose (n = 172)

Reason for non-adherence	Frequency (n)	Percentage (%)
Forgot vaccination appointment	60	34.9
Vaccine stock-out at health facility	49	28.5
Lack of transport to health facility	27	15.7
Caregiver not around at time of appointment	13	7.6
Caregiver busy with work/family duties	10	5.8
Advised by health worker not to vaccinate	9	5.2
Child was sick at scheduled visit	4	2.3
Child got malaria after vaccination	4	2.3
Partner refused further vaccination	4	2.3
Other vaccinated children still got malaria	3	1.7

The frequencies do not add up to 172 because these are multiple-response data

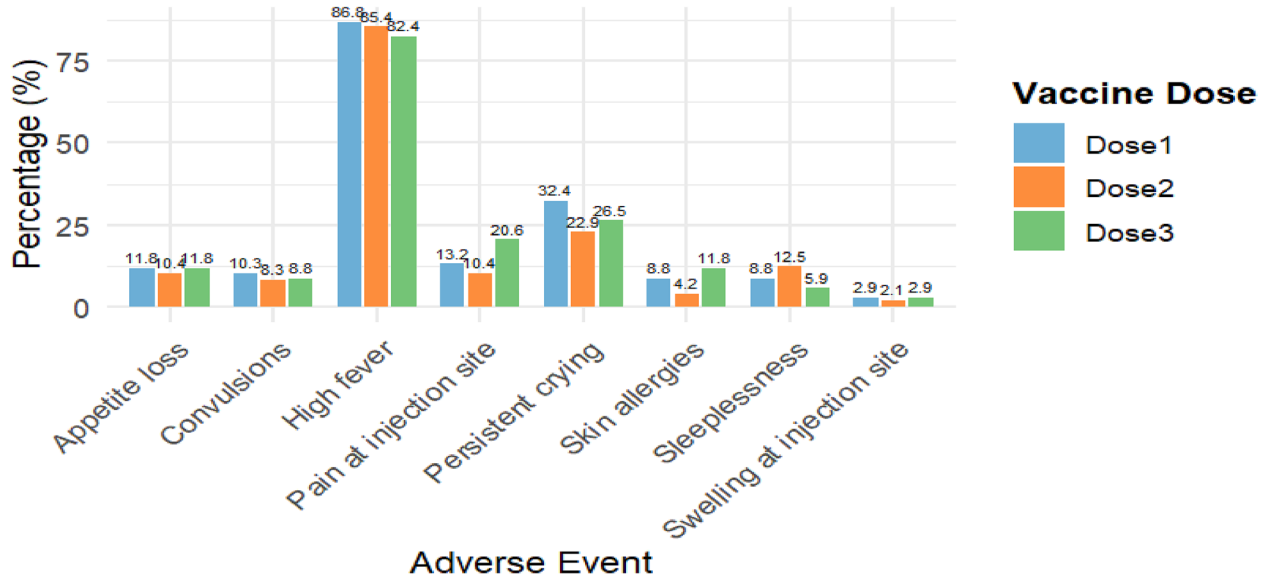


Fig. 2 Unverified caregiver-reported symptoms following malaria vaccination. Percentages describe symptoms among children reported to have experienced a reaction after each dose, rather than among all vaccine recipients. Reports were not clinically verified and do not establish causation or estimate adverse-event incidence

Other reasons, including caregiver unavailability where they were physically absent, being busy with competing household or livelihood responsibilities, advised by the health worker not to vaccinate in cases where vaccination was postponed because the child was deemed temporarily unfit, were reported by fewer than 10% of respondents each (Table 4).

Caregivers reported post vaccination reactions

Caregivers reported at least one reaction following R21/Matrix-M vaccination in 68 children after dose one, 48 after dose two and 34 after dose three. The symptoms were caregiver-reported, were not clinically confirmed and could not be established as causally attributable to vaccination. High fever was reported in 59/68 (86.8%), 41/48 (85.4%) and 28/34 (82.4%) children with reported reactions, respectively. Other reported symptoms included sleeplessness, convulsions, and skin allergies (Fig. 2).

These percentages describe the distribution of symptoms among children with reported reactions, rather than symptom frequency among all dose recipients. High fever reflected caregivers' descriptions rather than clinical diagnoses.

Factors associated with dose three completion

The adjusted analysis included 727 children across 30 villages; six children had missing responses on vaccine unavailability. The model adjusted for caregiver age, sex, education, occupation, walking time, caregiver-reported vaccine unavailability and health-worker reminders, with village-clustered standard errors. Caregiver-reported vaccine unavailability was significantly associated with lower three-dose completion (aPR 0.64). Completion was higher in the 0.5–1-h walking-time category than in the <0.5-h category (aPR 1.21), although walking time was not statistically significant overall. No other adjusted comparisons were statistically significant (Table 5).

Sensitivity analyses

Removing each covariate individually produced changes below 10% in most remaining prevalence ratios. The estimate for tertiary versus no formal education increased from 1.18 to 1.34 when occupation was omitted and decreased to 1.05 when caregiver-reported vaccine unavailability was omitted, representing changes of 13.6% and 11.1%, respectively. The vaccine-unavailability estimate changed by less than 1% across individual omissions.

Qualitative results

Socio-demographic characteristics of the KII, IDI and FGD participants (n = 55)

Qualitative participants were aged 20–46 years (mean 29.7 years, standard deviation 7.2). Of 55 participants, 33 (60.0%) were female, 28 (50.9%) had primary education, 40 (72.7%) were farmers and 29 (52.7%) were Anglican or Protestant (Table 6).

Qualitative analysis identified two overarching themes: factors supporting completion and barriers to completion. Participants described perceived benefits, motivation, scheduling information and community support as helpful. Reported barriers included missed appointments, competing responsibilities, service unavailability, difficult journeys, safety concerns, rumours and limited partner assistance.

Theme 1: Promoters of malaria vaccine adherence and completion

Sub-theme 1.1 Reduced malaria episodes encouraged completion

Caregivers consistently linked vaccination to visible improvements in child health, noting fewer malaria episodes after the first dose. The positive change attributed to the vaccine motivated them to return for subsequent doses, as they believed the vaccine was effective. Some echoed that the vaccine reduces the severity of the disease.

> *"Since my child received the malaria vaccine, he does not fall sick as before… that is why I made sure to bring him for the second and third doses."* (IDI, Participant 06, caregiver)

The focus group discussion also echoed similar sentiments:

> *"For me I heard people are in joyousness and being grateful that this vaccine has really helped them. They say because of the vaccine even if their children get malaria, it's not really severe. Personally, I am also very happy because if I compare the rate at which my child used to fall sick with malaria it's not like today."* (FGD, Group 3, Participant 05, caregiver)

Table 5 Crude and adjusted prevalence ratios for three-dose malaria vaccine completion

Characteristic	Total, n	Completed, n	Not completed, n	cPR (95% CI)	Crude p-value	aPR (95% CI)	Adjusted p-value
Child age, months							
≤12	402	239	163	1.00		1.00	
>12	325	168	157	0.87 (0.73–1.04)	0.124	0.86 (0.73–1.02)	0.077
Child sex							
Female	394	227	167	1.00		1.00	
Male	333	180	153	0.94 (0.85–1.04)	0.229	0.94 (0.86–1.03)	0.204
Caregiver age, years							
≤25	425	235	190	1.00		1.00	
26–35	248	140	108	1.02 (0.89–1.18)	0.775	1.02 (0.91–1.16)	0.692
≥36	54	32	22	1.07 (0.84–1.38)	0.586	1.09 (0.85–1.39)	0.510
Caregiver sex							
Female	688	385	303	1.00		1.00	
Male	39	22	17	1.01 (0.72–1.41)	0.963	1.02 (0.73–1.42)	0.926
Education							
No formal education	32	18	14	1.00		1.00	
Primary	557	306	251	0.98 (0.67–1.42)	0.901	1.05 (0.77–1.44)	0.743
Secondary	117	69	48	1.05 (0.67–1.63)	0.835	1.07 (0.72–1.58)	0.747
Tertiary	21	14	7	1.19 (0.77–1.83)	0.441	1.19 (0.73–1.94)	0.494
Occupation							
Peasant farmer	608	330	278	1.00		1.00	
Business	58	34	24	1.08 (0.85–1.37)	0.532	1.08 (0.86–1.36)	0.503
Civil servant	15	10	5	1.23 (0.85–1.77)	0.268	1.14 (0.68–1.91)	0.630
Other: casual labourer, tailor or salon worker	46	33	13	1.32 (1.05–1.66)	0.016	1.24 (0.98–1.58)	0.076
Walking time to nearest healthcare facility[1]							
<0.5 h	101	50	51	1.00		1.00	
0.5–1 h	380	226	154	1.20 (1.01–1.43)	0.039	1.21 (1.01–1.44)	0.038
>1 h	246	131	115	1.08 (0.83–1.40)	0.586	1.07 (0.83–1.39)	0.597
Caregiver-reported vaccine unavailability							
No	524	327	197	1.00		1.00	
Yes	203	80	123	0.63 (0.43–0.93)	0.021	0.64 (0.44–0.93)	0.020
Receipt of health-worker reminders							
No	334	177	157	1.00		1.00	
Yes	393	230	163	1.10 (0.91–1.33)	0.305	1.09 (0.91–1.30)	0.337

cPR crude prevalence ratio; *aPR* adjusted prevalence ratio; *CI* confidence interval. Analyses included 727 complete cases and were unweighted. The adjusted model included all listed variables. Crude and adjusted models used village-clustered robust standard errors across 30 villages. P-values were category-specific; the overall adjusted walking-time Wald p-value was 0.074

Sub-theme 1.2 Peace of mind and responsible parenting

Vaccination was described as reducing anxiety and giving caregivers peace of mind about their children's health. Many regarded completing the schedule as part of responsible parenting and ensuring family stability.

Table 6 Socio-demographic characteristics of respondents enrolled in the qualitative study (n = 55)

Variable	Category	Frequency (n)	Percentage (%)
Sex	Female	33	60.0
	Male	22	40.0
Age	20–24 years	15	27.3
	25–29 years	13	23.6
	30–34 years	6	10.9
	≥ 35 years	21	38.2
Education	None	2	3.6
	Primary	28	50.9
	Secondary	17	30.9
	Tertiary/Diploma	6	10.9
	Other (Tailoring/skills)	2	3.6
Religion	Anglican/Protestant	29	52.7
	Catholic	24	43.6
	Pentecostal	2	3.6
Profession	Farmer	40	72.7
	Midwife/Nurse	2	3.6
	Tailor	1	1.8
	Other (VHT/casual worker)	12	21.8

"What I know about this malaria vaccine is that it helps our children to stay healthy and also enable us to remain peaceful. When children are vaccinated fully, they do not fall sick as before." (FGD, Group 2, Participant 01, caregiver)
"I thought when I vaccinate my child, he will grow up without getting malaria at all. That encouraged me to complete all the doses." (IDI, Participant 07, caregiver)
"I took my child for the first malaria vaccine and made sure to return for the next ones. As a parent, I know vaccines protect children, so I don't want mine to miss." (FGD, Group 1, Participant 02, caregiver)

Sub-theme 1.3 Following schedules and reminders

Caregivers reported strong adherence to vaccination schedules, often guided by written return dates on cards and verbal instructions from health workers. They made deliberate efforts not to miss appointments despite challenges such as distance.

"They give you days, and I have to follow them strictly. Since my child started, I have not missed any appointment." (IDI, Participant 08, caregiver)
"Health workers told us that if you don't finish the doses, it will bring problems. That made me determined to complete all four." (KII, Participant 04, caregiver)

Sub-theme 1.4 Community and health worker support reinforced timeliness

Many participants mentioned that the health workers and neighbours played a crucial role in reminding caregivers of vaccination days. Some said community announcements by VHT mobilization also supported timely attendance, and this collective reinforcement reduced missed appointments. A member of the FGD had the following to say:

"The health worker reminded me to come back, and that helped me not to forget. Without reminders, many of us would miss." (FGD, Group 1, Participant 05, caregiver)

Sub-theme 1.5 Health facilities provided dose scheduling information

Some caregivers reported being informed at health facilities about the need to return for additional doses. A female participant had the following to say:

> *"I took my child to the health centre for vaccination and that is when I was told it is a malaria vaccine. They told me I should keep taking the child back for other doses."* (FGD, Group 3, Participant 03, caregiver)

Health workers interviewed also echoed similar sentiments. Some reported that they usually explain to the caregivers when they should return for the subsequent doses. One health worker said:

> *"When we give them the first dose, we explain clearly the date for the next dose and why it is important to complete all three doses. Most of them come back when they understand."* (KII, Participant 05, health worker)

Sub-theme 1.6 Adherence despite side effects

Despite side effects, many caregivers reported continuing with the vaccination because they valued protection against malaria. They believed temporary discomfort was preferable to severe illness.

> *"Even if the vaccine disturbs our children, we will still take the kids… They say it is better for the child to cry than to suffer from malaria."* (FGD, Group 3, Participant 03, caregiver)

Sub-theme 1.7 Community and religious encouragement

Community leaders, churches, and VHTs actively encouraged vaccination. The caregivers described that the announcements made during gatherings encouraged vaccination and reinforced its importance among the local communities.

> *"At church they announce that children should be taken for malaria vaccination. When you hear it from the churches, you know it is important."* (KII, Participant 01, caregiver)

Theme 2: Barriers to malaria vaccine adherence and completion

Sub-theme 2.1 Forgetfulness and competing responsibilities

Household duties, especially farming, often led caregivers to forget the subsequent vaccination appointments. Caregivers reported that competing responsibilities were a common reason for missing appointments.

> *"I was busy in the garden and forgot the date they gave me. By the time I remembered, the day had already passed."* (FGD, Group 1, Participant 06, caregiver)

Sub-theme 2.2 Vaccine stock-outs

Unavailability of the malaria vaccine during visits may have discouraged many caregivers, particularly after long walks to facilities. Some of the caregivers explained that these service delivery challenges disrupted adherence.

> *"I came to the health facility for the second dose but they told me there was no vaccine. I had to return again after 2 weeks, and that discouraged me."* (IDI, Participant 09, Caregiver)

Sub-theme 2.3 Transport and distance challenges

Long distances and lack of transport were significant barriers to completing doses. Caregivers described fatigue and difficulty carrying children on foot to the health facilities for vaccination.

> *"The health centre is far and I have no money for transport. Carrying the child on foot is difficult, so sometimes I miss the appointment."* (FGD, Group 4, Participant 05, caregiver)

Sub-theme 2.4 Overcrowding at the health facilities

Caregivers reported that overcrowding at health facilities discouraged them from completing malaria vaccine doses. Caregivers echoed that long waiting times and congested clinics often led some parents to give up and return home without vaccinating their children.

> *"Sometimes the clinic is very crowded and people wait for many hours. Some caregivers give up and go back home without vaccinating their children."* (KII, Participant 04, Health worker)

Sub-theme 2.5 Illness of the child at malaria vaccine schedule

Participants reported that community concerns about the malaria vaccine safety when the child is ill of any disease at vaccine schedule as a major contributor to decisions not to return for later doses. Some of the community members link the subsequent illness of their children after vaccination to the malaria vaccine.

> *"Some mothers saying the vaccine really disturbs their children and can be dangerous when the child is already sick.....some were even saying they will not take their children for vaccination again. They think the vaccine is the cause of sickness."* (FGD, Group 3, Participant 02, caregiver)

Sub-theme 2.6 Fever and swelling at injection site discouraged continuation

Minor side effects reported, such as fever and swelling, caused fear among some of the caregivers. Some of the caregivers delayed or missed subsequent doses due to concerns about their child's reaction. A caregiver of the child had the following to say:

> *"My child developed fever and cried the whole night after the first dose. I became scared and thought maybe the vaccine was not good."* (IDI, Participant 10, Caregiver)

Sub-theme 2.7 Rumours and community fears

Rumours about adverse events that were circulating in the communities, discouraged some caregivers from returning. Some of the people often misinterpreted side effects of the vaccines as signs of sickness, increasing fears and amplifying rumours about the vaccine.

> *"Some neighbours say vaccination swells the child's arm,..... so they don't take theirs. That discouraged a few people from taking their children for malaria vaccination."* (FGD, Group 3, Participant 07, caregiver)

Sub-theme 2.8 Gender roles and household decision-making

Women were primarily responsible for taking children for vaccination, often without support from husbands. The participants echoed that male involvement was limited, though some provided transport or encouragement.

"I am the one who decides everything about the child's health. My husband does not remind me or give money,..... I dig to get money myself." (IDI, Participant 11, caregiver)

FGDs revealed that women were primarily responsible for ensuring children's vaccination, with men only occasionally accompanying them. Participants emphasized that women carried the burden of adherence, while family acceptance was reflected in the absence of conflict after vaccination. As one participant explained:

"Sometimes men take the children, but mostly it is women. If you see no quarrel at home after vaccination, it means the family has welcomed it." (FGD, Group 1, Participant 01, caregiver)

To make integration of the quantitative and qualitative findings explicit, we developed a convergence matrix *(supplementary file 4)*. Statistical associations and qualitative accounts were presented separately before assessing convergence, complementarity and divergence. Reminders were described as helpful qualitatively, but the adjusted quantitative analysis did not demonstrate an association with completion. Confidence and community support remained qualitative findings. The GRAMMS reporting framework [25] informed the presentation of design and integration.

Discussion

Overall adherence and timeliness of malaria vaccine completion

This study extended evidence on R21/Matrix-M initiation in Kole and Kwania districts by examining continuation among eligible initiators. The companion uptake study reported initiation among 48.3% of eligible children [26], whereas the present study assessed three-dose completion among children who had initiated vaccination at least 3 months earlier. The distinct denominators precluded direct coverage comparisons or calculation of population-level completion. Together, these findings pointed to separate challenges in initiation and continuation, consistent with multi-dose programme experience in Ghana, Kenya and Malawi [14, 15, 27]. Non-completion at one survey could reflect delay rather than permanent discontinuation.

Timeliness among recipients with available records suggested that scheduled return was achievable for many families who attended subsequent visits. This did not explain the experience of recipients with missing dates or children who had not received later doses. Differences in schedules, timing definitions and follow-up limited direct comparison with RTS,S implementation studies [14, 27]. Programmes should assess both delayed vaccination and interruptions in attendance, rather than treating timely receipt among attenders as evidence that initiators generally remained on schedule.

Perceived vaccine benefits and caregiver confidence

In the survey, 40.2% of caregivers reported malaria in their child after vaccination. These unverified reports could not estimate vaccine effectiveness or establish vaccine failure because episode timing, diagnostic confirmation and dose status at illness were uncertain. R21/Matrix-M trial evidence showed reduced clinical malaria rather than complete protection [8]. Qualitative accounts separately described reassurance and "peace of mind" when caregivers perceived fewer malaria episodes. These perceptions may have supported confidence, but they did not demonstrate a quantitative association with completion. The companion awareness, knowledge and perceptions study provided complementary context on caregiver understanding [16]. Counselling should explain both benefits and limits of vaccination and reinforce continued malaria prevention, prompt diagnosis and effective treatment [24].

Forgetfulness, competing responsibilities and the role of reminder systems

Forgetting appointments was the most frequently reported reason among children with exactly two doses, but it was not analysed as a predictor in the final model. Qualitative accounts linked missed appointments to farming and household responsibilities, suggesting that attendance could be disrupted despite willingness to vaccinate. Health-worker reminders were not significantly associated with completion after adjustment, although participants described reminders as helpful. This divergence could reflect differences in reminder timing, targeting or measurement; it did not confirm a reminder effect. Longitudinal implementation research similarly described practical pressures affecting continued attendance [14, 27, 28]. Clear return dates, flexible service arrangements and reminder strategies were plausible responses requiring implementation assessment.

Perceived side effects and continued vaccine acceptance

Caregiver-reported symptoms and qualitative accounts of safety concerns highlighted the importance of risk communication. Some participants continued vaccination despite reported discomfort, whereas others described fear and delayed attendance. These contrasting accounts suggested that perceived benefits and concerns could coexist; they did not show that reactions rarely deterred completion. Similar qualitative implementation research described the importance of trust and interpretation of symptoms [14, 27]. Communication should distinguish expected reactions from symptoms requiring assessment, acknowledge concerns and avoid attributing unverified illnesses to vaccination.

Reports of fever and convulsions required cautious interpretation because they were not clinically verified and lacked sufficient diagnostic and temporal information. Symptom percentages among children reporting reactions did not represent incidence among all vaccine recipients. The survey could not classify reported convulsions as febrile seizures, adjudicate causation or determine the vaccine's safety or benefit–risk balance. Trial and surveillance evidence provided external context [8, 29–31], but could not validate individual reports in this cross-sectional sample. Programme communication should encourage reporting and appropriate clinical assessment without presenting these survey percentages as confirmed vaccine-event rates.

Vaccine availability and health system barriers affecting adherence

Caregiver-reported vaccine unavailability was associated with lower completion after adjustment. Qualitative descriptions of unsuccessful visits and discouragement provided a plausible explanation for interrupted attendance, consistent with service-delivery constraints described in Ghana and Kenya [13, 14, 32]. However, unavailability was not verified against facility stock records, and caregivers of non-completers may have recalled failed visits more readily. Temporal ambiguity and differential recall limited causal interpretation. Reliable vaccine supply, clear information about service availability and follow-up after unsuccessful visits were plausible programme responses that warranted local evaluation.

Geographical access and transport challenges

Walking time showed no statistically significant overall adjusted association with completion, although the 0.5–1-h category had higher completion than the <0.5-h category. The absence of a clear distance gradient suggested that walking time alone did not capture the practical burden of access. Qualitative accounts described transport costs, difficult journeys and fatigue, complementing rather than confirming the quantitative findings. Similar implementation studies described interactions between travel and service constraints [14, 33]. Reliable services and targeted outreach or transport support should therefore be guided by locally documented barriers rather than an assumed distance effect.

Social and gender influences shaping adherence

Women comprised most surveyed caregivers, while qualitative accounts described a substantial burden of organising vaccination alongside domestic and livelihood responsibilities. Caregiver sex was not significantly associated with completion in the adjusted model, so the qualitative accounts concerned caregiving roles rather than a demonstrated sex effect. Some participants described limited partner assistance, whereas others reported transport help or encouragement. Community and household support have similarly featured in qualitative vaccination research [28, 34]. Locally acceptable approaches to shared caregiving and practical support warranted assessment, without assuming that male-involvement interventions would improve completion.

Study limitations

Several limitations affected interpretation. Restricting enrolment to vaccine initiators meant that district-wide coverage and experiences of non-initiators could not be assessed. Fixed village recruitment targets, six neighbouring-village additions and household substitution could have produced unequal selection probabilities and selection bias; community recruitment did not eliminate these limitations. Estimates were unweighted, and village-clustered standard errors addressed within-village dependence rather than selection bias. Differences in documentation and incomplete timing information could have affected outcome classification; second-dose timing was unavailable for 21.9% of recipients. Caregiver-reported exposures and symptoms were subject to recall, misclassification and social desirability bias. Differential recall of unsuccessful visits among non-completers could have exaggerated the unavailability association, but its direction could not be established without validation. Cross-sectional measurement and uncertain exposure timing limited causal interpretation, and residual confounding by time since initiation, district or programme exposure remained possible. The original sample-size calculation did not incorporate clustering, limiting the basis for anticipated power; analysis could not restore that planned precision. Inference also relied on independence between 30 villages, which could be imperfect where villages shared facilities or administrative units. No screened child was excluded because of a severe adverse-event history. Qualitative transcripts were not returned for participant validation.

Conclusion and recommendation

Just over half of sampled vaccine initiators eligible for dose three had completed the initial R21/Matrix-M series by the survey date. Caregiver-reported vaccine unavailability was associated with lower completion, while qualitative accounts identified practical constraints, confidence, and sources of support. Reliable vaccine availability, clear scheduling information, and locally appropriate outreach, reminder, and household-support strategies warrant implementation assessment. Longitudinal studies should examine delayed completion, the full four-dose schedule and the effectiveness of these programme responses.

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Author contributions SSP conceptualized the study, designed the methodology, led data collection, analysis, and drafted the initial manuscript. JNK, MO, AY, GS, RI and JIN provided guidance on study design, and contributed to interpretation of findings. SSP, SIA, JA, DLE, ZN and RA supported qualitative analysis. SSP supported data collection supervision, quantitative data management and statistical analysis and manuscript revision. JNK provided overall scientific oversight,

contributed to the interpretation of results, and critically revised the manuscript for intellectual content. All authors read and approved the final manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate The ethical approval for this study was received from the Makerere University School of Medicine Research and Ethics Committee (Mak-SOMREC) under approval number Mak-SOMREC-2024-938. We further obtained clearance from the Uganda National Council for Science and Technology (UNCST) under approval number HS5968ES. Written informed consent was obtained from all participants prior to their involvement in the study. For participants with limited literacy, the consent process was conducted orally in the presence of a witness, and documented accordingly with a thumbprint. All methods were carried out in accordance with relevant guidelines and regulations of the Declaration of Helsinki.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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Authors and Affiliations

Sean Steven Puleh[1,2] · Moses Ocan[3] · Godfrey Siu[4] · Adoke Yeka[5,6] · Joaniter I. Nankabirwa[1,5] · Richard Idro[7] · Stella Immaculate Akech[1,2] · Joy Acen[1] · David L. Ejalu[1] · Ziadah Nankinga[1] · Robert Afayo[1] · Joan N. Kalyango[1,8]

✉ Sean Steven Puleh
spuleh@lirauni.ac.ug

1 Clinical Epidemiology Unit, School of Medicine, Makerere University College of Health Sciences, Kampala City, Uganda

2 Department of Epidemiology and Biostatistics, Faculty of Public Health, Lira University, Lira City, Uganda

3 Department of Pharmacology and Therapeutics, Makerere University College of Health Sciences, Kampala City, Uganda

4 Department of Child Health and Development Centre, College of Health Sciences, Makerere University, Kampala City, Uganda

5 Infectious Diseases Research Collaboration (IDRC), Kampala City, Uganda

6 Department of Disease Control and Environmental Health, School of Public Health, Makerere University College of Health Sciences, Kampala City, Uganda

7 Department of Paediatrics and Child Health, College of Health Sciences, Makerere University, Kampala City, Uganda

8 Department of Pharmacy, Makerere University College of Health Sciences, Kampala City, Uganda