Supplementary Tables

Table of contents

Table.S1 Detail of visit dates used as the end of observation window[1]

Date	Description
2B0	- Recorded on the day of the second booster vaccination - Recorded prior to the time of the second booster vaccination - 365 days after the first booster vaccination
B365	- 365 days after the first booster vaccination - For participants that did not take part in the 2-year extension of the trial
B1Y	- 365 days after the first booster vaccination - Same time as B365 - For participants that agreed and confirmed to take part in trial extension
Study exit date	- For participants withdrawn from the study due to loss to follow up, death, etc

[1]The use of follow up visit dates as the end of observation window followed the priority order of using 2B0, B365, B1Y, exit date. One participant did not have any recorded follow-up visit dates because the scheduled 2B0 pre-vaccination visit was not conducted due to ongoing serious adverse events. For this participant, the end date was calculated as 365 days after the first booster vaccination.

Table.S2 Baseline characteristics of participants included in analysis, stratified by vaccination group, transmission setting and site

	Total number of participants	Number of male participants	Number of female participants	Average age[1] (days)	Average duration of observation window (days)
All sites (n=4369)					
Control	1442	754 (52.3%)[2]	688 (47.7%)	587.0	767.6
R21/Matrix-M	2927	1517 (51.8%)	1410 (48.2%)	591.3	766.0
Seasonal sites (n=2239)					
Control	745	391 (52.5%)	354 (47.5%)	573.1	781.0
R21/Matrix-M	1494	783 (52.4%)	711 (47.6%)	573.2	780.3
Perennial sites (n=2130)					
Control	697	363 (52.1%)	334 (47.9%)	602.0	753.4
R21/Matrix-M	1433	734 (51.2%)	699 (48.8%)	610.3	751.0
Nanoro site (n=559)					
Control	181	93 (51.4%)	88 (48.6%)	565.4	794.5
R21/Matrix-M	378	194 (51.3%)	184 (48.7%)	555.3	789.3
Siglé site (n=568)					
Control	192	100 (52.1%)	92 (47.9%)	559.1	794.9
R21/Matrix-M	376	198 (52.7%)	178 (47.3%)	569.9	793.1
Bougouni site (n=1112)					
Control	372	198 (53.2%)	174 (46.8%)	584.0	767.3
R21/Matrix-M	740	391 (52.8%)	349 (47.2%)	584.0	769.3
Dandé site (n=1063)					
Control	349	182 (52.1%)	167 (47.9%)	631.4	745.6
R21/Matrix-M	714	369 (51.7%)	345 (48.3%)	639.6	744.5
Bagamoyo site (n=515)					
Control	162	88 (54.3%)	74 (45.7%)	582.0	772.6
R21/Matrix-M	353	177 (50.1%)	176 (49.9%)	592.7	764.3
Kilifi site (n=552)					
Control	186	93 (50.0%)	93 (50.0%)	564.2	751.1
R21/Matrix-M	366	188 (51.4%)	178 (48.6%)	570.2	750.9

[1]Age was recorded at the time of the first vaccine dose administration.

[2]Percentages for male and female participants are shown in parentheses and calculated within each respective vaccination group.

Table.S3 Multivariable mixed-effect logistic and negative binomial regression analysis for predictors of systemic antibiotic usage showing association between different covariates and risk of systemic antibiotic prescription across all sites

Variable	Logistic regression[3]		Negative binomial regression for rate[4]	
	Adjusted odds ratio[1] (95% CI)	*p*-value	Adjusted incidence rate ratio[2] (95% CI)	*p*-value
Vaccination group				
Control	Reference	–	Reference	–
R21/Matrix-M	0.91 (0.74 – 1.11)	0.343	0.95 (0.90 – 0.99)	0.029
Age group				
0 – 1 years old	Reference	–	Reference	–
1 – 2 years old	0.66 (0.51 – 0.86)	0.002	0.88 (0.76 – 1.03)	0.121
2 – 3 years old	0.44 (0.34 – 0.56)	<0.001	0.66 (0.51 – 0.85)	0.001
Sex				
Female	Reference	–	Reference	–
Male	1.14 (0.95 – 1.38)	0.161	1.07 (1.02 – 1.12)	0.003

Abbreviations: CI confidence interval

[1,2]Ratios were calculated with respect to the reference group, adjusted for age, sex, site-level random effects.

[3]Results were calculated with robust standard errors. The model included site-level random intercept only.

[4]Results were calculated with robust standard errors. The model included site-level random intercept, and site-level random slope for covariate age group.

Table.S4 Multivariable mixed-effect logistic and negative binomial regression analysis for predictors of antibiotic usage showing association between different covariates and risk of antibiotic prescription, stratified by transmission setting

	Logistic regression[3]		Negative binomial regression for rate[4]	
Variable	**Adjusted odds ratio[1] (95% CI)**	***p*-value**	**Adjusted incidence rate ratio[2] (95% CI)**	***p*-value**
Seasonal sites				
Vaccination group				
Control	Reference	–	Reference	–
R21/Matrix-M	1.37 (0.93 – 2.01)	0.113	0.96 (0.91 – 1.02)	0.195
Age group				
0 – 1 years old	Reference	–	Reference	–
1 – 2 years old	0.65 (0.38 – 1.11)	0.119	0.84 (0.79 – 0.90)	<0.001
2 – 3 years old	0.43 (0.26 – 0.71)	0.001	0.59 (0.55 – 0.63)	<0.001
Sex				
Female	Reference	–	Reference	–
Male	1.36 (0.93 – 1.99)	0.107	1.04 (0.99 – 1.10)	0.134
Perennial sites				
Vaccination group				
Control	Reference	–	Reference	–
R21/Matrix-M	0.78 (0.62 – 1.00)	0.046	0.92 (0.84 – 1.00)	0.062
Age group				
0 – 1 years old	Reference	–	Reference	–
1 – 2 years old	0.69 (0.51 – 0.93)	0.016	0.97 (0.71 – 1.31)	0.826
2 – 3 years old	0.46 (0.34 – 0.63)	<0.001	0.77 (0.46 – 1.29)	0.314
Sex				
Female	Reference	–	Reference	–
Male	1.06 (0.85 – 1.32)	0.608	1.12 (1.03 – 1.21)	0.009

Abbreviations: CI confidence interval

[1,2]Ratios were calculated with respect to the reference group, adjusted for age, sex, site-level random effects.

[3]Results were calculated with robust standard errors. Models for both transmission settings included site-level random intercept only.

[4]Results were calculated with robust standard errors. The model for seasonal sites included site-level random intercept only. The model for perennial sites included site-level random intercept, and site-level random slope for covariate age group.

Table.S5 Multivariable mixed-effect Cox regression analysis for predictors of antibiotic usage showing association between different covariates and risk of antibiotic prescription, stratified by transmission setting

Variable	Time to first antibiotic prescription[3]		Recurrent antibiotic prescription[4]	
	Adjusted hazard ratio[1] (95% CI)	*p*-value	Adjusted hazard ratio[2] (95% CI)	*p*-value
Seasonal sites				
Vaccination group				
Control	Reference	–	Reference	–
R21/Matrix-M	1.02 (0.93 – 1.11)	0.715	0.99 (0.95 – 1.03)	0.661
Age group				
0 – 1 years old	Reference	–	Reference	–
1 – 2 years old	0.86 (0.78 – 0.96)	0.005	0.87 (0.83 – 0.91)	<0.001
2 – 3 years old	0.68 (0.61 – 0.76)	<0.001	0.63 (0.60 – 0.66)	<0.001
Sex				
Female	Reference	–	Reference	–
Male	1.03 (0.95 – 1.12)	0.493	1.02 (0.98 – 1.06)	0.414
Perennial sites				
Vaccination group				
Control	Reference	–	Reference	–
R21/Matrix-M	0.92 (0.82 – 1.02)	0.120	0.95 (0.90 – 1.01)	0.287
Age group				
0 – 1 years old	Reference	–	Reference	–
1 – 2 years old	0.81 (0.71 – 0.93)	0.002	0.86 (0.80 – 0.92)	0.003
2 – 3 years old	0.62 (0.54 – 0.71)	<0.001	0.62 (0.58 – 0.67)	<0.001
Sex				
Female	Reference	–	Reference	–
Male	1.11 (1.00 – 1.24)	0.049	1.10 (1.04 – 1.16)	0.032

Abbreviations: CI confidence interval

[1,2]Ratios were calculated with respect to the reference group, adjusted for age, sex.

[3]Results were calculated from the standard Cox proportional hazards model. The model stratified baseline hazards by sites.

[4]Results were calculated from the recurrent event Andersen-Gill Cox model. The model stratified baseline hazards by sites and included frailty terms to account for repeated events for each individual, addressing heterogeneity and variability across individuals.

Table.S6 Multivariable mixed-effect Cox regression analysis for predictors of systemic antibiotic usage showing association between different covariates and risk of systemic antibiotic prescription across all sites

Variable	Time to first antibiotic prescription[3]		Time to recurrent antibiotic prescriptions[4]	
	Adjusted hazard ratio[1] (95% CI)	*p*-value	Adjusted hazard ratio[2] (95% CI)	*p*-value
Vaccination group				
Control	Reference	–	Reference	–
R21/Matrix-M	0.97 (0.91 – 1.04)	0.433	0.98 (0.94 – 1.01)	0.288
Age group				
0 – 1 years old	Reference	–	Reference	–
1 – 2 years old	0.84 (0.78 – 0.92)	<0.001	0.86 (0.83 – 0.89)	<0.001
2 – 3 years old	0.65 (0.60 – 0.71)	<0.001	0.62 (0.59 – 0.64)	<0.001
Sex				
Female	Reference	–	Reference	–
Male	1.06 (0.99 – 1.13)	0.101	1.05 (1.02 – 1.09)	0.019

Abbreviations: CI confidence interval

[1,2]Ratios were calculated with respect to the reference group, adjusted for age, sex.

[3]Results were calculated from the standard Cox proportional hazards model. The model stratified baseline hazards by sites.

[4]Results were calculated from the recurrent event Andersen-Gill Cox model. The model stratified baseline hazards by sites and included frailty terms to account for repeated events for each individual, addressing heterogeneity and variability across individuals.

Table.S7 Antibiotic prescriptions by antibiotic class and vaccination group across all sites

Class of antibiotics[1]	Incidence rate of antibiotic prescriptions per person-year		Proportion of antibiotic prescriptions[2]	
	Control	R21/Matrix-M	Control	R21/Matrix-M
Aminoglycosides	0.60	0.55	3.55%	3.41%
Ansamycins (rifamycin)	0.46	0.48	0.03%	0.07%
Antimalarial drug with sulfonamide	0.86	0.76	3.50%	1.37%
Beta-lactams (carbapenems)	0.00	0.46	0.00%	0.01%
Beta-lactams (cephalosporins)	0.67	0.70	2.88%	3.09%
Beta-lactams (penicillin)	1.21	1.20	43.58%	43.90%
Fluoroquinolones	0.62	0.64	2.56%	2.93%
Fusidanes	0.46	0.46	0.13%	0.16%
Glycopeptides	0.00	0.46	0.00%	0.01%
Mupirocin	0.46	0.46	0.02%	0.01%
Nitroimidazoles	0.78	0.80	14.28%	15.50%
Phenicols	0.49	0.48	0.02%	0.01%
Polyketides (macrolides)	0.94	0.91	23.49%	23.64%
Polyketides (tetracyclines)	0.66	0.59	2.69%	2.61%
Polypeptides & aminoglycosides[3]	0.59	0.57	1.06%	0.98%
Polypeptides & polyketides (tetracyclines)[3]	0.00	0.49	0.00%	0.01%
Sulfonamide	0.56	0.53	0.25%	0.23%
Trimethoprim & sulfonamide[3]	0.57	0.55	1.97%	2.04%

[1]Classification details are provided in Table.S8.

[2]Proportions represent the percentage of total antibiotic prescriptions belonging to each class within the control and R21/Matrix-M groups.

[3]Drugs with components of 2 antibiotic classes.

Table.S8 Classes and examples of antibiotics prescribed in the trial

Class[1]	**Examples**
Aminoglycosides	Neomycin
	Gentamicin
	Framycetin
	Tobramycin
Ansamycins	Rifamycin
Antimalarial combination therapy with sulfanomide	Madar: sulfadoxine + pyrimethamine
	Co-arinate: artesunate + sulfamethoxypyrazine + pyrimethamine
Beta-lactams (carbapenems)	Imipenem
Beta-lactams (cephalosporins)	Cephalexin
	Cefadroxil
	Ceftriaxone
	Cefixime
	Cefotaxime
	Cefuroxime
Beta-lactams (penicillin)	Amoxicillin
	Flucloxacillin
	Ampicillin
	Cloxacillin
	Benzyl penicillin (penicillin g)
	Phenoxymethylpenicillin (penicillin v)
	Augmentin
	Cloxacillin
Fluoroquinolones	Ciprofloxacin
	Norfloxacin
	Ofloxacin
Fusidanes	Fusidic acid
Glycopeptides	Vancomycin
Mupirocin	Mupirocin (pseudomonic acid a)
Nitroimidazoles	Metronidazole
Phenicols	Chloramphenicol
Polyketides - type I (macrolides/ketolides)	Azithromycin
	Erythromycin
	Josamycin
Polyketides – type II (tetracyclines)	Tetracycline
	Doxycycline
	Oxytetracycline
Polypeptides	Bacitracin
	Polymyxin
Polypeptides & aminoglycosides[2]	Auricap: Dexamethasone + Polymyxin B + Neomycin

Class[1]	**Examples**
Polypeptides & aminoglycosides[2]	Antibio synalar: Fluocinolone acetonide + Polymyxin B sulfate + Neomycin sulfate Baneocin: Bacitracin + Neomycin Maxidrol: Dexamethasone + Polymyxin B + Neomycin Polydexa: Dexamethason + Polymyxin B + Neomycin
Polypeptides & polyketides (tetracyclines)[2]	Auricularum: Nystatin + Polymyxin + Dexamethasone + Oxytetracycline
Sulfanomide	Sulfamethoxypyrazine Silver sulfadiazine Sulfamethoxazole Sulfadoxine
Trimethoprim	Trimethoprim

[1]Classified based on chemical structure and mechanism of action according to standard guidelines (1,2).
[2]Drugs with combination of different antibiotic classes are listed with drug names and ingredients.

Table.S9 Antibiotic prescriptions by diagnostic reason and vaccination group across all sites

Diagnostic category	Incidence rate of antibiotic prescriptions per person-year		Proportion of antibiotic prescriptions[2]	
	Control	R21/Matrix-M	Control	R21/Matrix-M
Anaemia	0.95	0.74	0.12%	0.09%
Arthritis	0.00	0.46	0.00%	0.01%
Burn, trauma and wound	0.60	0.62	2.19%	2.27%
Ear	0.83	0.93	3.95%	4.59%
Febrile	0.48	0.53	0.34%	0.30%
Gastrointestinal	0.82	0.82	13.94%	14.70%
Genitourinary	0.55	0.64	0.33%	0.59%
Gland	0.50	0.51	0.42%	0.40%
Hepatic	0.46	0.95	0.01%	0.02%
Immunological	0.53	0.66	0.33%	0.32%
Malaria	0.85	0.75	3.17%	1.21%
Measles	0.45	0.71	0.03%	0.05%
Mental	0.48	0.00	0.01%	0.00%
Neurological	0.46	0.64	0.01%	0.03%
Nutritional and metabolic	0.71	0.68	0.07%	0.07%
Ophthalmic	0.70	0.74	4.01%	4.07%
Oral and dental	0.50	0.58	0.30%	0.18%
Respiratory	1.82	1.77	59.15%	59.91%
Septicemia	1.41	0.61	0.04%	0.03%
Skin and soft tissue	0.90	0.88	10.64%	10.47%
Typhoid	0.79	0.44	0.12%	0.02%
Unspecified infection	0.50	0.52	0.31%	0.30%
Other	0.61	0.58	0.48%	0.40%

[1]Proportions represent the percentage of total antibiotic prescriptions belonging to each diagnostic category within the control and R21/Matrix-M groups.

Table.S10 Antibiotic prescriptions by antibiotic class and vaccination group, stratified by transmission setting

Class of antibiotics[1]	Incidence rate of antibiotic prescriptions per person-year				Proportion of antibiotic prescriptions[2]			
	Seasonal sites		Perennial sites		Seasonal sites		Perennial sites	
	Control	R21/Matrix-M	Control	R21/Matrix-M	Control	R21/Matrix-M	Control	R21/Matrix-M
Aminoglycosides	0.58	0.53	0.64	0.59	3.56%	3.55%	3.52%	3.12%
Ansamycins (rifamycin)	0.46	0.48	0.00	0.00	0.05%	0.10%	0.00%	0.00%
Antimalarial drug with sulfonamide	0.86	0.76	0.00	0.00	5.26%	2.04%	0.00%	0.00%
Beta-lactams (carbapenems)	0.00	0.46	0.00	0.00	0.00%	0.01%	0.00%	0.00%
Beta-lactams (cephalosporins)	0.68	0.70	0.60	0.68	3.51%	3.65%	1.61%	1.94%
Beta-lactams (penicillin)	1.21	1.22	1.21	1.18	40.30%	40.82%	50.10%	50.23%
Fluoroquinolones	0.61	0.61	0.63	0.69	2.32%	2.64%	3.02%	3.52%
Fusidanes	0.46	0.46	0.00	0.49	0.20%	0.22%	0.00%	0.03%
Glycopeptides	0.00	0.46	0.00	0.00	0.00%	0.01%	0.00%	0.00%
Mupirocin	0.00	0.00	0.46	0.46	0.00%	0.00%	0.05%	0.03%
Nitroimidazoles	0.83	0.84	0.66	0.66	17.00%	18.50%	8.85%	9.44%
Phenicols	0.00	0.00	0.49	0.48	0.00%	0.00%	0.05%	0.03%
Polyketides (macrolides)	0.89	0.86	1.02	1.00	22.11%	22.62%	26.26%	25.73%
Polyketides (tetracyclines)	0.68	0.60	0.59	0.52	3.18%	3.28%	1.71%	1.24%
Polypeptides & aminoglycosides	0.59	0.57	0.00	0.00	1.59%	1.45%	0.00%	0.00%
Polypeptides & polyketides (tetracyclines)	0.00	0.49	0.00	0.00	0.00%	0.01%	0.00%	0.00%
Sulfonamide	0.00	0.00	0.56	0.53	0.00%	0.00%	0.75%	0.70%
Trimethoprim & sulfonamide	0.54	0.51	0.59	0.58	0.91%	1.09%	4.07%	4.01%

[1]Classification details are provided in Table.S8.

[2]Proportions represent the percentage of total antibiotic prescriptions belonged to each class within the control and R21/Matrix-M groups.

Table.S11 Antibiotic prescriptions by diagnostic reason for prescription and vaccination group, stratified by transmission setting

Diagnostic category	Incidence rate of antibiotic prescriptions per person-year				Proportion of antibiotic prescriptions[1]			
	Seasonal sites		Perennial sites		Seasonal sites		Perennial sites	
	Control	R21/Matrix-M	Control	R21/Matrix-M	Control	R21/Matrix-M	Control	R21/Matrix-M
Anaemia	1.88	0.57	0.64	0.96	0.09%	0.06%	0.16%	0.13%
Arthritis	0.00	0.46	0.00	0.00	0.00%	0.01%	0.00%	0.00%
Burn, trauma and wound	0.56	0.56	0.68	0.72	2.12%	2.21%	2.30%	2.39%
Ear	0.78	0.88	0.92	1.02	3.93%	4.70%	3.99%	4.38%
Febrile	0.47	0.47	0.48	0.53	0.02%	0.04%	0.90%	0.77%
Gastrointestinal	0.86	0.86	0.71	0.72	16.50%	17.33%	9.46%	9.93%
Genitourinary	0.61	0.71	0.49	0.51	0.31%	0.68%	0.37%	0.44%
Gland	0.47	0.49	0.52	0.52	0.28%	0.27%	0.66%	0.63%
Hepatic	0.46	0.95	0.00	0.00	0.02%	0.02%	0.00%	0.00%
Immunological	0.00	1.22	0.53	0.62	0.00%	0.06%	0.90%	0.79%
Malaria	0.86	0.75	0.49	0.49	4.92%	1.86%	0.12%	0.04%
Measles	0.45	0.71	0.00	0.00	0.05%	0.07%	0.00%	0.00%
Mental	0.48	0.00	0.00	0.00	0.02%	0.00%	0.00%	0.00%
Neurological	0.46	0.00	0.00	0.64	0.02%	0.00%	0.00%	0.09%
Nutritional and metabolic	0.71	0.62	0.00	0.98	0.12%	0.08%	0.00%	0.04%
Ophthalmic	0.69	0.72	0.74	0.78	4.10%	4.12%	3.87%	3.96%
Oral and dental	0.47	0.51	0.54	0.73	0.24%	0.17%	0.41%	0.20%
Respiratory	1.72	1.70	1.99	1.89	55.39%	57.13%	65.71%	64.95%
Septicemia	1.41	0.74	0.00	0.47	0.07%	0.02%	0.00%	0.04%
Skin and soft tissue	0.95	0.90	0.82	0.83	10.99%	10.64%	10.03%	10.15%
Typhoid	0.59	0.47	1.57	0.41	0.12%	0.01%	0.12%	0.02%
Unspecified infection	0.47	0.71	0.52	0.50	0.12%	0.04%	0.66%	0.77%
Other	0.57	0.56	0.78	0.63	0.56%	0.47%	0.33%	0.28%

[1]Proportions represent the percentage of total antibiotic prescriptions belonged to each diagnostic category within the control and R21/Matrix-M groups.

Table.S12 Malaria treatment metrics by vaccination group, study site, and transmission setting

	Participants received at least 1 malaria treatment	Participants received more than 1 malaria treatment	Average incidence rate of malaria treatment (number of treatments/ person-year)[2]	Average time to first malaria treatment (days)[3]	Average time interval until malaria treatment (days)[4]	Average time interval between each malaria treatment (days)
All sites (n=4369)						
Control	939 (65.1%)[1]	869 (60.3%)	1.82 (5566/ 3030.6)	199.9	320.0	50.0
R21/Matrix-M	1057 (36.1%)	912 (31.2%)	0.64 (3952/ 6138.4)	283.6	347.4	37.8
Seasonal sites (n=2239)						
Control	572 (76.8%)	552 (74.1%)	2.58 (4144/1593.0)	160.8	308.6	49.1
R21/Matrix-M	653 (43.7%)	590 (39.5%)	0.85 (2710/3191.9)	263.1	341.2	41.5
Perennial sites (n=2130)						
Control	367 (52.7%)	317 (45.5%)	1.00 (1422/1437.6)	260.8	337.8	51.7
R21/Matrix-M	404 (28.2%)	322 (22.5%)	0.42 (1242/2946.5)	316.7	357.4	31.0
Nanoro site (n=559)						
Control	170 (93.9%)	167 (92.3%)	4.37 (1722/393.7)	117.5	313.8	53.4
R21/Matrix-M	282 (74.6%)	263 (69.6%)	1.79 (1451/816.8)	235.0	344.2	53.7
Siglé site (n=568)						
Control	172 (89.6%)	170 (88.5%)	3.06 (1279/417.8)	136.8	303.1	50.1
R21/Matrix-M	191 (50.8%)	178 (47.3%)	0.86 (699/816.4)	273.6	338.3	33.8
Bougouni site (n=1112)						
Control	230 (61.8%)	215 (57.8%)	1.47 (1143/781.4)	210.7	309.0	45.0
R21/Matrix-M	180 (24.3%)	149 (20.1%)	0.36 (560/1558.7)	295.9	339.7	29.2
Dandé site (n=1063)						
Control	235 (67.3%)	205 (58.7%)	1.20 (858/712.5)	249.6	328.5	53.5
R21/Matrix-M	236 (33.1%)	189 (26.5%)	0.43 (629/1455.4)	320.7	347.3	20.9
Bagamoyo site (n=515)						
Control	57 (35.2%)	45 (27.8%)	0.84 (283/342.7)	268.8	355.8	50.6
R21/Matrix-M	88 (24.9%)	71 (20.1%)	0.52 (373/738.6)	302.3	380.9	53.3
Kilifi site (n=552)						
Control	75 (40.3%)	67 (36.0%)	0.73 (281/382.5)	289.9	353.1	46.7
R21/Matrix-M	80 (21.9%)	62 (16.9%)	0.32 (240/752.4)	320.9	361.3	36.1

[1]Percentages are shown in parentheses and calculated within each respective vaccination group.

[2]Duration of observation window was adjusted from days to years through multiplication by 365.25.

[3,4]Time was calculated from the administration date of the third dose in the primary series vaccine.

Table.S13 Multivariable mixed-effect logistic and negative binomial regression analysis for predictors of malaria treatment showing association between different covariates and risk of malaria treatment across all sites and stratified by transmission setting

	Logistic regression[3]		Negative binomial regression for rate[4]	
Variable	**Adjusted odds ratio[1] (95% CI)**	***p*-value**	**Adjusted incidence rate ratio[2] (95% CI)**	***p*-value**
All sites				
Vaccination group				
Control	Reference	–	Reference	–
R21/Matrix-M	0.25 (0.21 – 0.28)	<0.001	0.34 (0.31 – 0.38)	<0.001
Age group				
0 – 1 years old	Reference	–	Reference	–
1 – 2 years old	1.66 (1.40 – 1.98)	<0.001	1.38 (1.22 – 1.56)	<0.001
2 – 3 years old	2.24 (1.88 – 2.67)	<0.001	1.49 (1.31 – 1.69)	<0.001
Sex				
Female	Reference	–	Reference	–
Male	1.26 (1.10 – 1.44)	0.001	1.15 (1.05 – 1.27)	0.004
Seasonal sites				
Vaccination group				
Control	Reference	–	Reference	–
R21/Matrix-M	0.17 (0.13 – 0.21)	<0.001	0.29 (0.26 – 0.33)	<0.001
Age group				
0 – 1 years old	Reference	–	Reference	–
1 – 2 years old	1.78 (1.40 – 2.26)	<0.001	1.31 (1.14 – 1.51)	<0.001
2 – 3 years old	2.77 (2.16 – 3.56)	<0.001	1.44 (1.25 – 1.67)	<0.001
Sex				
Female	Reference	–	Reference	–
Male	1.34 (1.10 – 1.63)	0.004	1.14 (1.02 – 1.28)	0.022
Perennial sites				
Vaccination group				
Control	Reference	–	Reference	–
R21/Matrix-M	0.34 (0.28 – 0.41)	<0.001	0.42 (0.35 – 0.50)	<0.001
Age group				
0 – 1 years old	Reference	–	Reference	–
1 – 2 years old	1.53 (1.19 – 1.97)	0.001	1.47 (1.17 – 1.85)	0.001
2 – 3 years old	1.84 (1.43 – 2.37)	<0.001	1.56 (1.24 – 1.96)	<0.001
Sex				
Female	Reference	–	Reference	–
Male	1.20 (1.00 – 1.45)	0.052	1.16 (0.98 – 1.38)	0.085

Abbreviations: CI confidence interval

[1,2]Ratios were calculated with respect to the reference group, adjusted for age, sex, site-level random effects.

[3]Results were calculated with robust standard errors. All models included site-level random intercept only.

[4]Results were calculated with robust standard errors. All models included site-level random intercept only.

Table.S14 Multivariable mixed-effect Cox regression analysis for predictors of malaria treatment showing association between different covariates and risk of malaria treatment across all sites and stratified by transmission setting

Variable	Time to first antibiotic prescription[3]		Recurrent antibiotic prescription[4]	
	Adjusted hazard ratio[1] (95% CI)	*p*-value	Adjusted hazard ratio[2] (95% CI)	*p*-value
All sites				
Vaccination group				
Control	Reference	–	Reference	–
R21/Matrix-M	0.34 (0.31 – 0.37)	<0.001	0.35 (0.33 – 0.37)	<0.001
Age group				
0 – 1 years old	Reference	–	Reference	–
1 – 2 years old	1.44 (1.28 – 1.62)	<0.001	1.41 (1.30 – 1.52)	<0.001
2 – 3 years old	1.74 (1.55 – 1.96)	<0.001	1.57 (1.45 – 1.70)	<0.001
Sex				
Female	Reference	–	Reference	–
Male	1.22 (1.11 – 1.33)	<0.001	1.15 (1.08 – 1.22)	0.003
Seasonal sites				
Vaccination group				
Control	Reference	–	Reference	–
R21/Matrix-M	0.30 (0.26 – 0.33)	<0.001	0.32 (0.30 – 0.34)	<0.001
Age group				
0 – 1 years old	Reference	–	Reference	–
1 – 2 years old	1.46 (1.26 – 1.68)	<0.001	1.37 (1.25 – 1.49)	<0.001
2 – 3 years old	1.82 (1.58 – 2.10)	<0.001	1.49 (1.36 – 1.63)	<0.001
Sex				
Female	Reference	–	Reference	–
Male	1.24 (1.11 – 1.39)	<0.001	1.11 (1.04 – 1.19)	0.040
Perennial sites				
Vaccination group				
Control	Reference	–	Reference	–
R21/Matrix-M	0.41 (0.35 – 0.47)	<0.001	0.41 (0.37 – 0.46)	<0.001
Age group				
0 – 1 years old	Reference	–	Reference	–
1 – 2 years old	1.41 (1.16 – 1.72)	0.001	1.49 (1.29 – 1.73)	0.001
2 – 3 years old	1.62 (1.33 – 1.98)	<0.001	1.73 (1.49 – 2.00)	<0.001
Sex				
Female	Reference	–	Reference	–
Male	1.18 (1.02 – 1.36)	0.022	1.17 (1.05 – 1.30)	0.071

Abbreviations: CI confidence interval

[1,2]Ratios were calculated with respect to the reference group, adjusted for age, sex.

[3]Results were calculated from the standard Cox proportional hazards model. The model stratified baseline hazards by sites.

[4]Results were calculated from the recurrent event Andersen-Gill Cox model. The model stratified baseline hazards by sites and included frailty terms to account for repeated events within each individual, addressing heterogeneity and variability across individuals.

References

1. REVIVE [Internet]. [cited 2025 May 4]. Classes of Antibiotics. Available from: https://revive.gardp.org/resource/classes-of-antibiotics/?cf=encyclopaedia

2. MSD Manual [Internet]. [cited 2025 May 4]. Overview of Antibiotics. Available from: https://www.msdmanuals.com/home/infections/antibiotics/overview-of-antibiotics