Main tables and figures

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$$p_{ij} = P(Y_{ij} = 1) \tag{1}$$

$$\begin{aligned}\text{logit}(p_{ij}) &= \log\left(\frac{p_{ij}}{1-p_{ij}}\right) \\ &= \beta_0 + \beta_1 \cdot vaccination\ status_{ij} + \beta_2 \cdot age\ group_{ij} + \beta_3 \cdot sex_{ij} + \\ &\quad u_{0j} + u_{1j} \cdot age\ group_{ij} + u_{2j} \cdot sex_{ij} + \epsilon_{ij}\end{aligned} \tag{2}$$

$$\lambda_{ij} = \mathbb{E}(Y_{ij}) \tag{3}$$

$$\begin{aligned}\log(\lambda_{ij}) &= \beta_0 + \beta_1 \cdot vaccination\ status_{ij} + \beta_2 \cdot age\ group_{ij} + \beta_3 \cdot sex_{ij} + \\ &\quad u_{0j} + u_{1j} \cdot age\ group_{ij} + u_{2j} \cdot sex_{ij} + \log\left(observation\ window\ length_{ij}\right)\end{aligned} \tag{4}$$

Table.1 Equation parameters of generalised linear mixed models

Parameters	**Definition**
Y_{ij}	Binary outcome of receiving at least 1 antibiotic prescription or not for participant i at site j
p_{ij}	Probability of receiving at least 1 antibiotic prescription for participant i at site j
λ_{ij}	Expected number of antibiotic prescriptions for participant i at site j
β_0	Intercept
$\beta_1, \beta_2, \beta_3$	Fixed effect coefficients
u_{0j}	Site-level random intercept
u_{1j}, u_{2j}	Potential site-level random slopes for age group and sex
ϵ_{ij}	Residual error
$\log\left(observation\ window\ length_{ij}\right)$	Offset term to account for varying length of observation window

$$S(t \mid vaccination\ status) = P(t_i > t) = \prod_{i:t_i \le t} (1 - \frac{d_i(vaccination\ status)}{n_i(vaccination\ status)}) \quad (5)$$

$$\mathrm{h}(t \mid vaccination\ status, age\ group, sex, site) =$$
$$h_0^{(site)}(t) \cdot \exp(\beta_1 \cdot vaccination\ status + \beta_2 \cdot age\ group + \beta_3 \cdot sex) \quad (6)$$

Table.2 Equation parameters of survival analysis and multivariable mixed-effect Cox regression model

Parameters	**Definition**
$S(t \mid vaccination\ status)$	Survival probability, probability of antibiotic prescriptions occurs after time t given vaccination status
t_i	Time points that antibiotic prescriptions occur
d_i	Number of antibiotic prescriptions at time t_i
n_i	Number of individuals at risk just before time t_i
$h_0^{(site)}(t)$	Baseline hazard function stratified by sites
$\beta_1, \beta_2, \beta_3$	Coefficients

Table.3 Antibiotic prescription metrics during the observation window by vaccination group, study site, and transmission setting

	Participants received at least 1 antibiotic prescription	Participants received more than 1 antibiotic prescription	Average incidence rate of antibiotic prescriptions (number of prescriptions/ person-year)[2]	Average time to first antibiotic prescription (days)[3]	Average time interval until antibiotic prescriptions (days)[4]	Average time interval between each antibiotic prescription (days)
All sites (n=4369)						
Control	1171 (81.2%)[1]	997 (69.1%)	1.95 (5946/3030.6)	139.4	303.1	118.9
R21/Matrix-M	2329 (79.6%)	1963 (67.1%)	1.84 (11363/6138.4)	145.9	306.9	118.9
Seasonal sites (n=2239)						
Control	699 (93.8%)	631 (84.7%)	2.48 (3958/1593.0)	117.0	297.8	108.0
R21/Matrix-M	1425 (95.4%)	1282 (85.8%)	2.40 (7644/3191.9)	124.4	302.7	114.7
Perennial sites (n=2130)						
Control	472 (67.7%)	366 (52.5%)	1.39 (1988/1437.6)	172.5	311.1	137.7
R21/Matrix-M	904 (63.1%)	681 (47.5%)	1.27 (3719/2946.5)	179.7	313.4	127.0
Nanoro site (n=559)						
Control	173 (95.6%)	160 (88.4%)	2.95 (1160/393.7)	131.7	339.5	93.2
R21/Matrix-M	368 (97.4%)	336 (88.9%)	2.66 (2164/816.8)	136.6	337.1	109.7
Siglé site (n=568)						
Control	178 (92.7%)	154 (80.2%)	2.14 (896/417.8)	115.9	277.6	107.9
R21/Matrix-M	357 (94.9%)	313 (83.2%)	2.01 (1631/816.4)	132.3	292.2	126.1
Bougouni site (n=1112)						
Control	348 (93.5%)	317 (85.2%)	2.43 (1902/781.4)	110.3	287.3	115.6
R21/Matrix-M	700 (94.6%)	633 (85.5%)	2.46 (3839/1558.7)	114.0	290.0	111.6
Dandé site (n=1063)						
Control	255 (73.1%)	186 (53.3%)	1.06 (755/712.5)	202.0	315.1	161.9
R21/Matrix-M	489 (68.5%)	328 (45.9%)	0.92 (1334/1455.4)	216.6	320.7	155.1
Bagamoyo site (n=515)						
Control	36 (22.2%)	8 (4.94%)	0.14 (49/342.7)	303.2	330.2	130.7
R21/Matrix-M	59 (16.7%)	19 (5.38%)	0.13 (93/738.6)	324.7	337.0	55.00
Kilifi site (n=552)						
Control	181 (97.3%)	172 (92.5%)	3.10 (1184/382.5)	104.9	301.6	111.9
R21/Matrix-M	356 (97.3%)	334 (91.3%)	3.05 (2292/752.4)	105.0	299.5	103.6

[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 vaccine dose in the primary series.

Table.4 Multivariable mixed-effect logistic and negative binomial regression analysis for predictors of antibiotic usage showing association between different covariates and risk of 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 – 1.12)	0.365	0.95 (0.90 – 0.99)	0.029
Age group				
0 – 1 years old	Reference	–	Reference	–
1 – 2 years old	0.68 (0.52 – 0.88)	0.004	0.89 (0.77 – 1.03)	0.111
2 – 3 years old	0.45 (0.35 – 0.59)	<0.001	0.66 (0.51 – 0.85)	0.001
Sex				
Female	Reference	–	Reference	–
Male	1.13 (0.94 – 1.37)	0.201	1.07 (1.02 – 1.12)	0.004

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

Variable	Time to first antibiotic prescription[3]		Time to recurrent antibiotic prescriptions[4]	
	Adjusted hazard ratio (95% CI)[1]	*p*-value	Adjusted hazard ratio (95% CI)[2]	*p*-value
Vaccination group				
Control	Reference	–	Reference	–
R21/Matrix-M	0.98 (0.91 – 1.05)	0.506	0.98 (0.94 – 1.01)	0.291
Age group				
0 – 1 years old	Reference	–	Reference	–
1 – 2 years old	0.84 (0.78 – 0.92)	<0.001	0.86 (0.83 – 0.90)	<0.001
2 – 3 years old	0.66 (0.61 – 0.72)	<0.001	0.62 (0.60 – 0.65)	<0.001
Sex				
Female	Reference	–	Reference	–
Male	1.06 (0.99 – 1.13)	0.082	1.05 (1.02 – 1.08)	0.026

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.

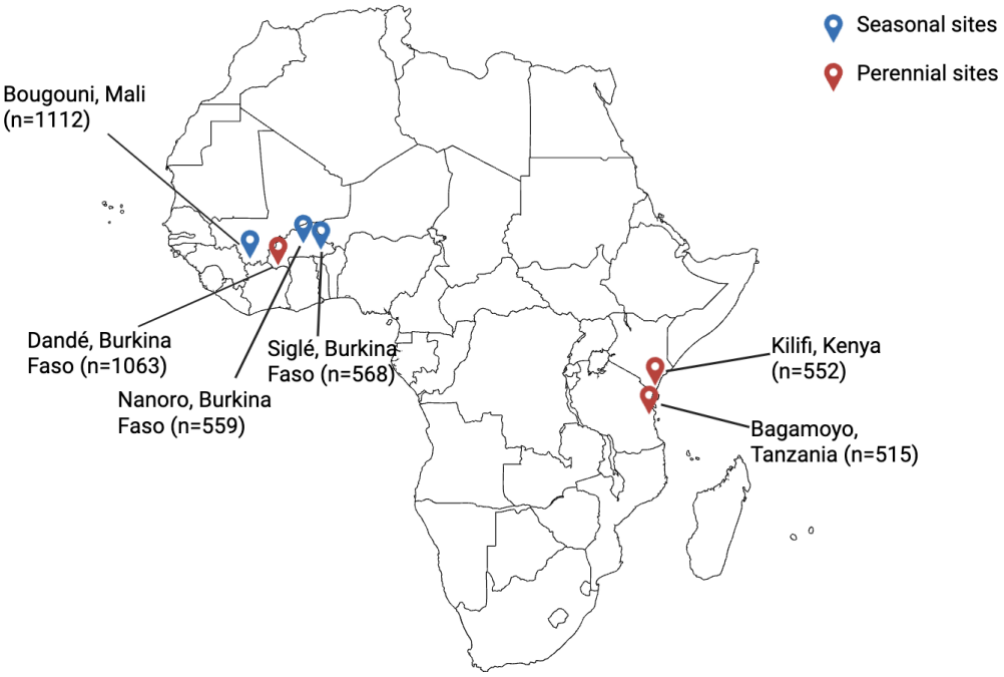

Figure.1 Map of clinical trial study sites, indicating sites with seasonal and perennial malaria transmission.

The definition of seasonal and perennial transmission sites was done by the clinical trial team through preliminary assessment of malaria prevalence and transmission level (8,30). The number of participants included in the analysis at each site is shown. At Nanoro site, participants were recruited, administered vaccines and recorded medication use at two clinics: one located in Nanoro and the other in Siglé, while other sites were conducted at one single clinic. Created with *BioRender*.

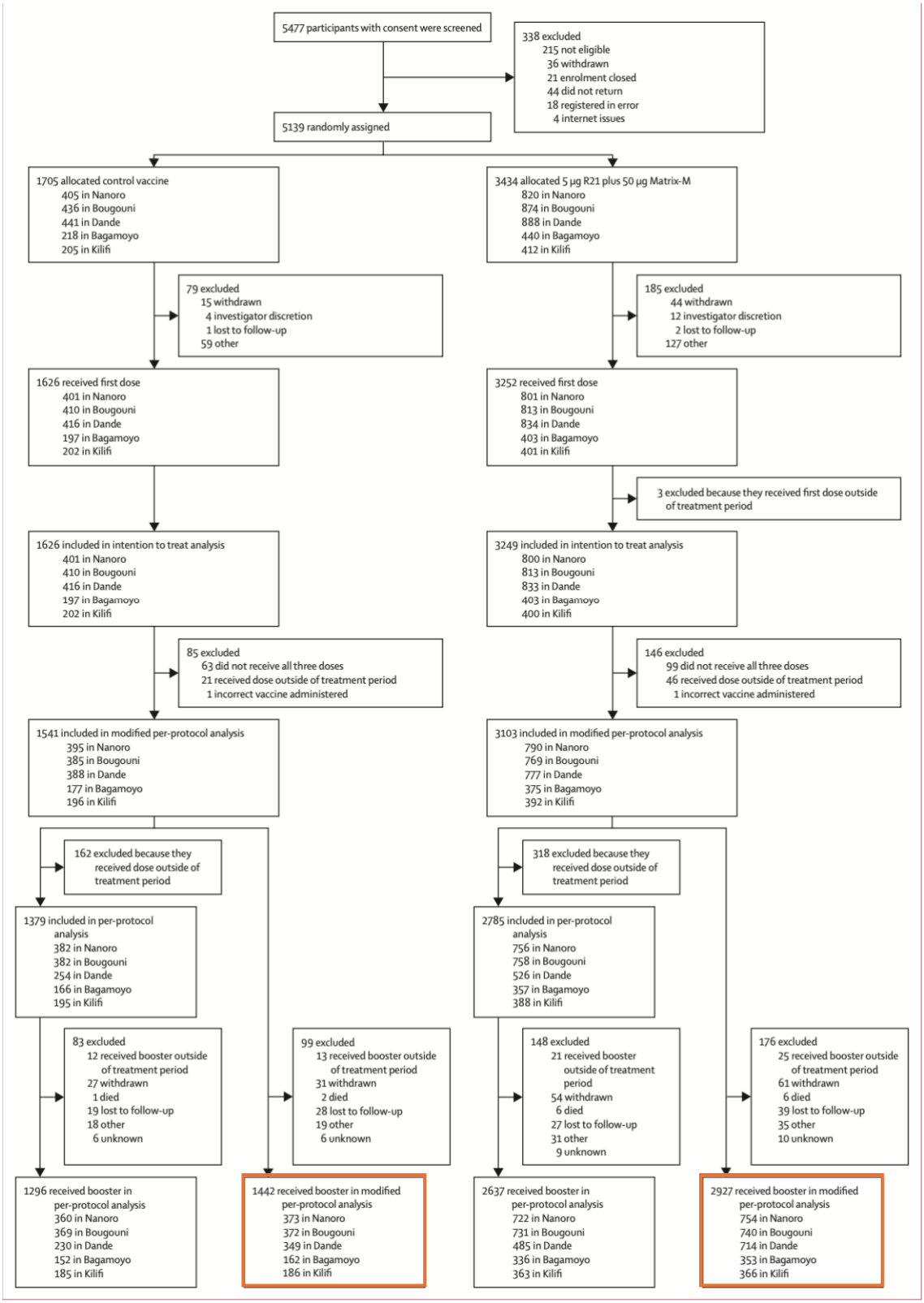

Figure.2 Flow chart of participant enrolment and vaccine administration in R21/Matrix-M and control vaccination group in the phase 3 clinical trial.

The orange-highlighted boxes indicated the study population used in this analysis: participants included in modified-per-protocol analysis, received three primary series doses and the first booster dose (total: n=4369; R21/Matrix-M group: n=2927; control group: n=1442). Adapted from Datoo et al. (8).

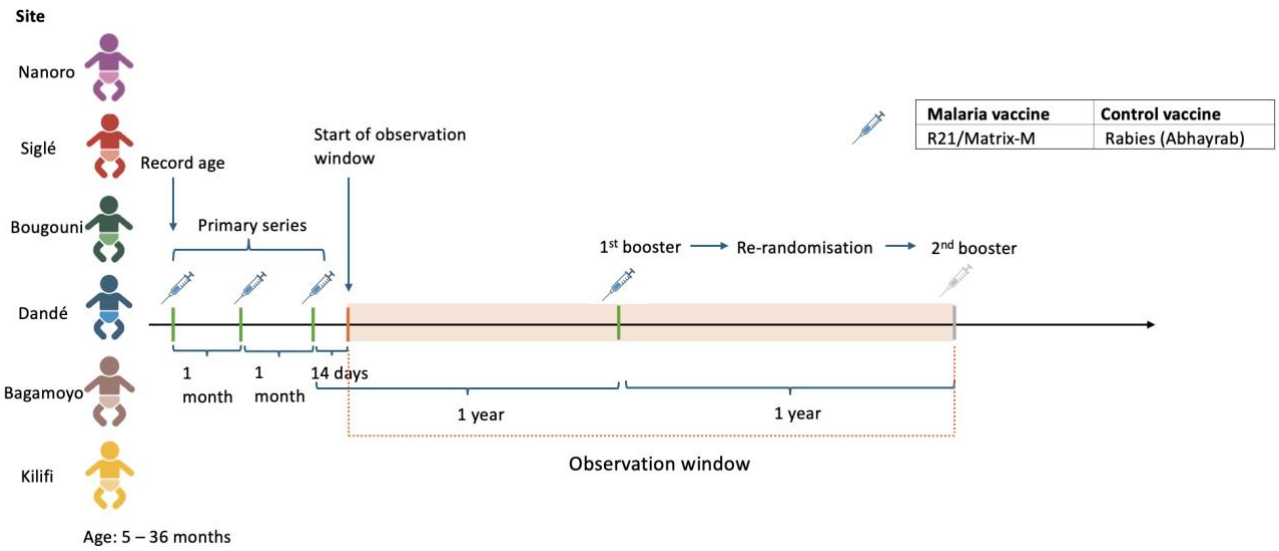

Figure.3 Vaccination dosing schedule and observation window.
The timeline illustrates the timing of primary series and booster doses vaccination, with the follow-up observation window for antibiotic usage outcome assessment highlighted in orange. The observation window started from 14 days after the third dose administration and ended before the second booster administration. The details of visit dates used as the end date of observation window are provided in the supplementary materials (Table.S1). Created with *BioRender*.

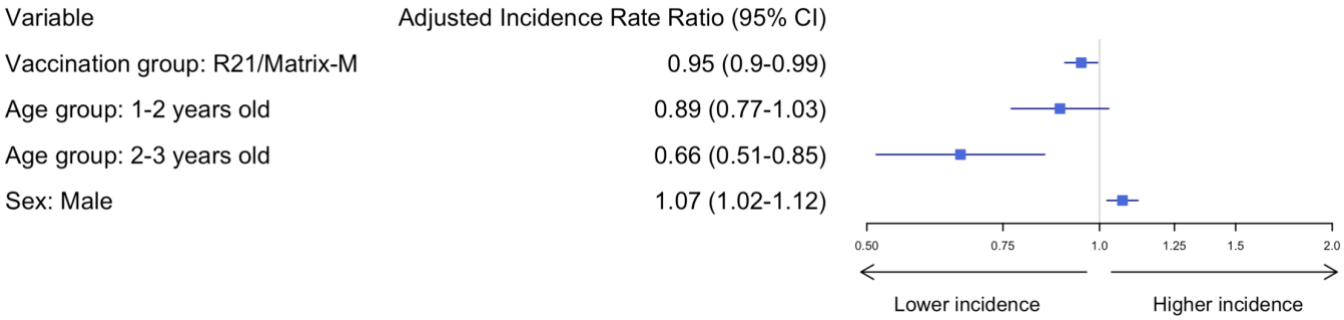

Figure.4 Forest plot of adjusted incidence rate ratio (aIRR) of antibiotic prescriptions for variables including vaccination group, age group and sex.

Estimates are shown on a logarithmic scale. Square boxes represent aIRR point estimates, horizontal lines indicate 95% confidence intervals. Estimates were calculated using the negative binomial regression model with person-year as an offset, adjusted for age, sex and site-level random effects. The reference level is control Rabies vaccinated group, age group – 0 to 1 year old, female. Vertical grey line at aIRR=1 represents no difference in incidence rate between groups. aIRR less than 1 indicate a lower incidence rate of antibiotic prescriptions relative to the reference group, aIRR higher than 1 indicate a higher incidence rate.

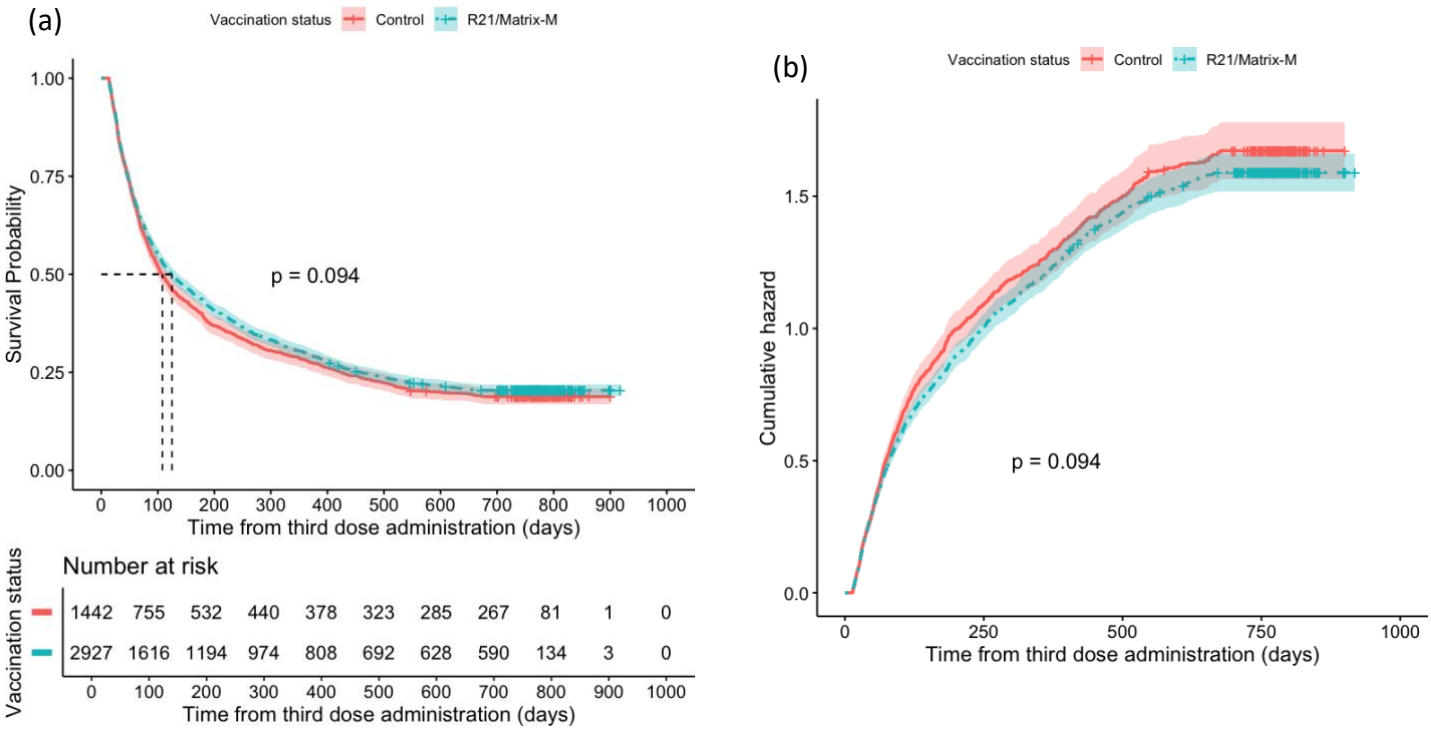

Figure.5 Kaplan-Meier estimates of time to first antibiotic prescription by vaccination group across all sites.

(a) Kaplan–Meier survival curves showing the probability of not receiving antibiotic prescription in the control and R21/Matrix-M groups. The number of individuals at risk at intervals of 100 days is shown in the risk table below the plot. **(b)** Cumulative hazard plot comparing the hazards of receiving an antibiotic prescription over time between vaccination groups. Time was calculated from the administration date of the third vaccine dose in the primary series. *p*-value is based on the log-rank test, comparing the survival times between two groups. Vertical bars on the curves represent censored individuals. Shades represent 95% confidence intervals. Dashed vertical and horizontal lines represent median survival.

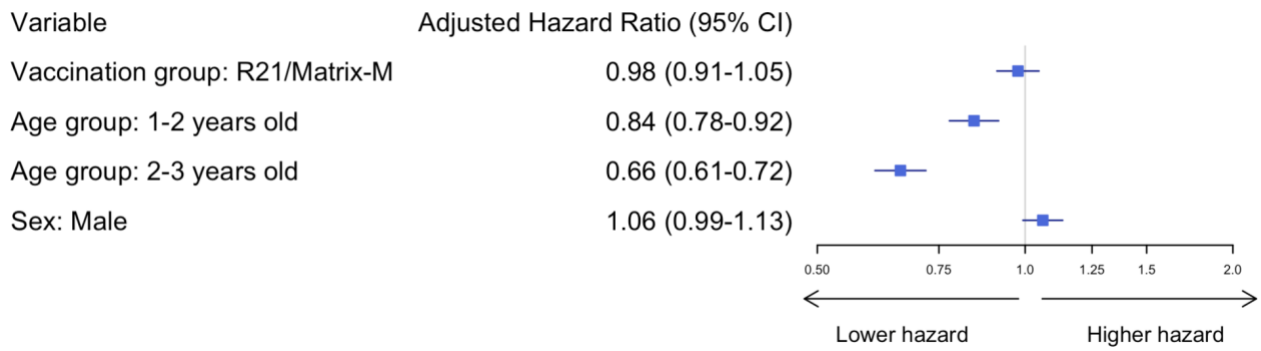

Figure.6 Forest plot of adjusted hazard ratio (aHR) of time to first antibiotic prescription for variables including vaccination group, age group and sex.
Estimates are shown on a logarithmic scale. Square boxes represent aHR point estimates, horizontal lines indicate 95% confidence intervals. Estimates were calculated using Cox regression models, adjusted for age, sex. The reference level is control Rabies vaccinated group, age group – 0 to 1 year old, female. Vertical grey line at aHR =1 represents no difference in time to first antibiotic prescription between groups. aHRs less than 1 indicate a lower hazard of antibiotic prescriptions relative to the reference group, aHRs higher than 1 indicate a higher hazard.

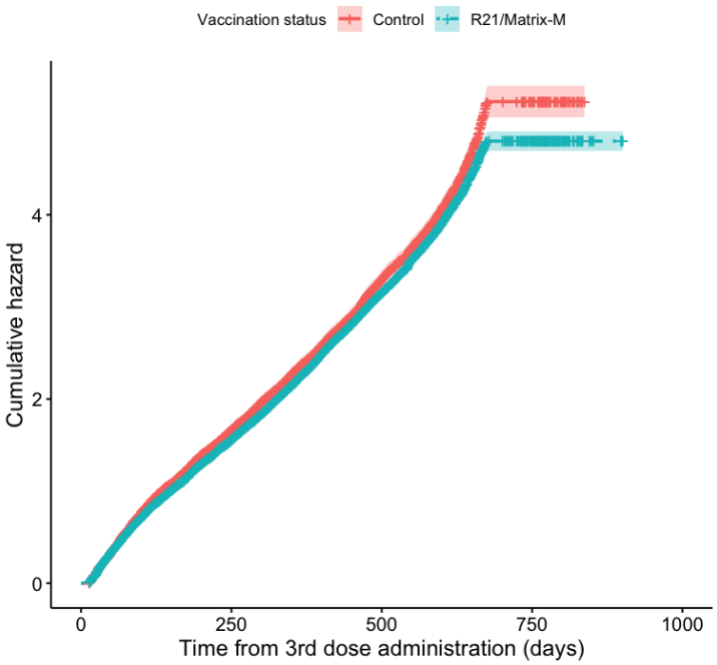

Figure.7 Kaplan-Meier estimates of time to recurrent antibiotic prescriptions by vaccination group across all sites.
Cumulative hazard plot comparing the hazards of receiving multiple repeated antibiotic prescriptions over time between vaccination groups. Time was calculated from the administration date of the third vaccine dose in the primary series. Vertical bar represents censored individuals. Shades represent 95% confidence intervals.

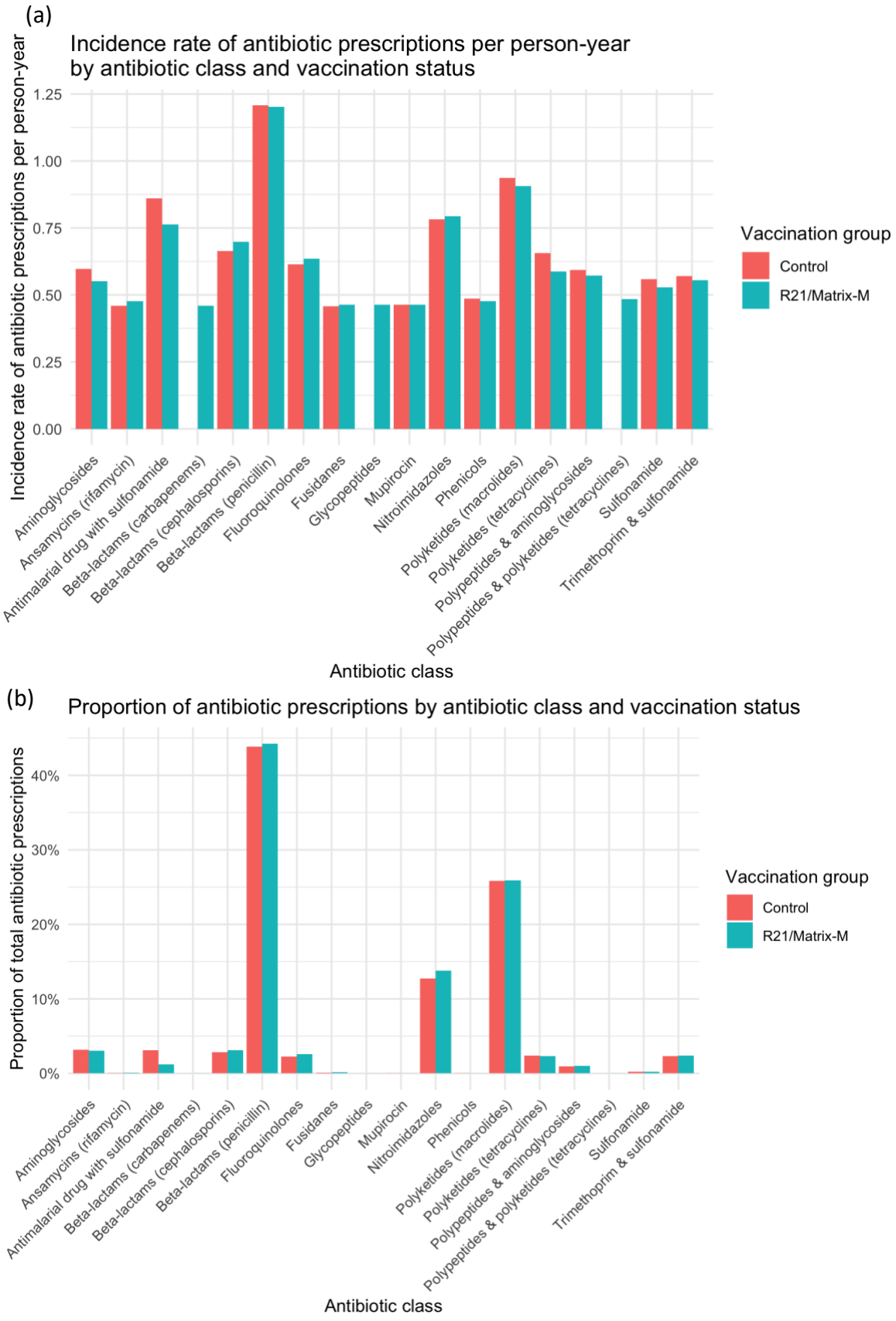

Figure.8 Antibiotic prescriptions by antibiotic class and vaccination group across all sites. **(a)** Incidence rate of antibiotic prescription per person-year of follow-up. **(b)** Proportion of total antibiotic prescriptions belonging to each class within the control and R21/Matrix-M groups. Classification details are provided in the supplementary materials (Table.S8).

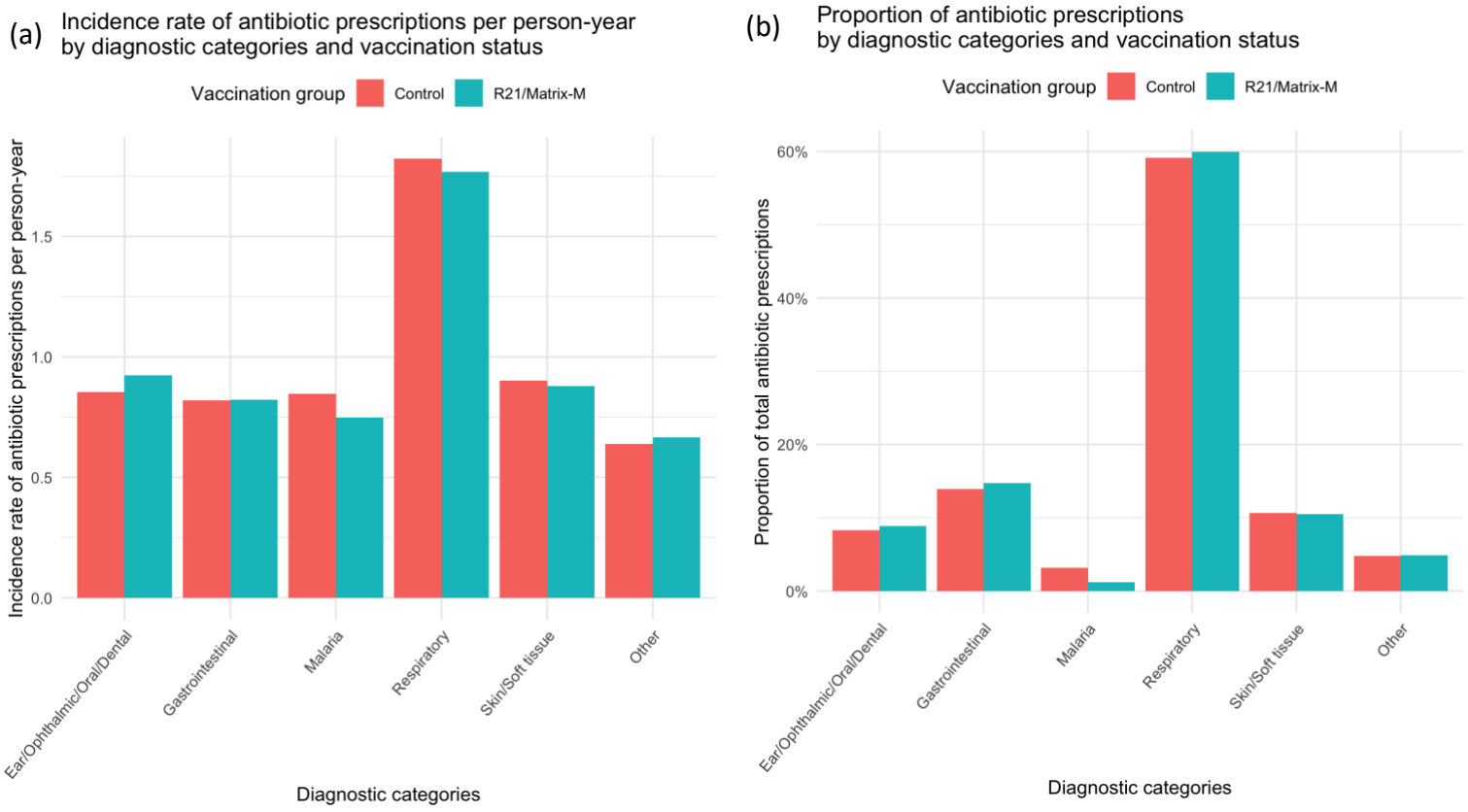

Figure.9 Antibiotic prescriptions by diagnostic reason and vaccination group across all sites.

(a) Incidence rate of antibiotic prescription per person-year of follow-up. **(b)** Proportion of total antibiotic prescriptions belonging to each diagnostic category within the control and R21/Matrix-M groups. Figures with more detailed and granular classification are provided in the supplementary materials (Figure.S8).