THE LANCET Infectious Diseases

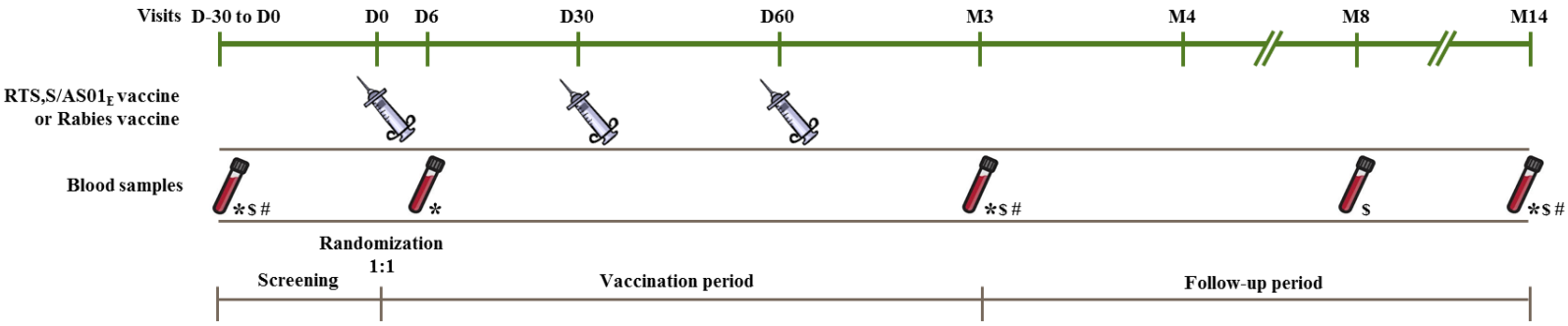
Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Otieno L, Oneko M, Otieno W, et al. Safety and immunogenicity of RTS,S/AS01 malaria vaccine in infants and children with WHO stage 1 or 2 HIV disease: a randomised, double-blind, controlled trial. *Lancet Infect Dis* 2016; published online July 6. http://dx.doi.org/10.1016/S1473-3099(16)30161-X.

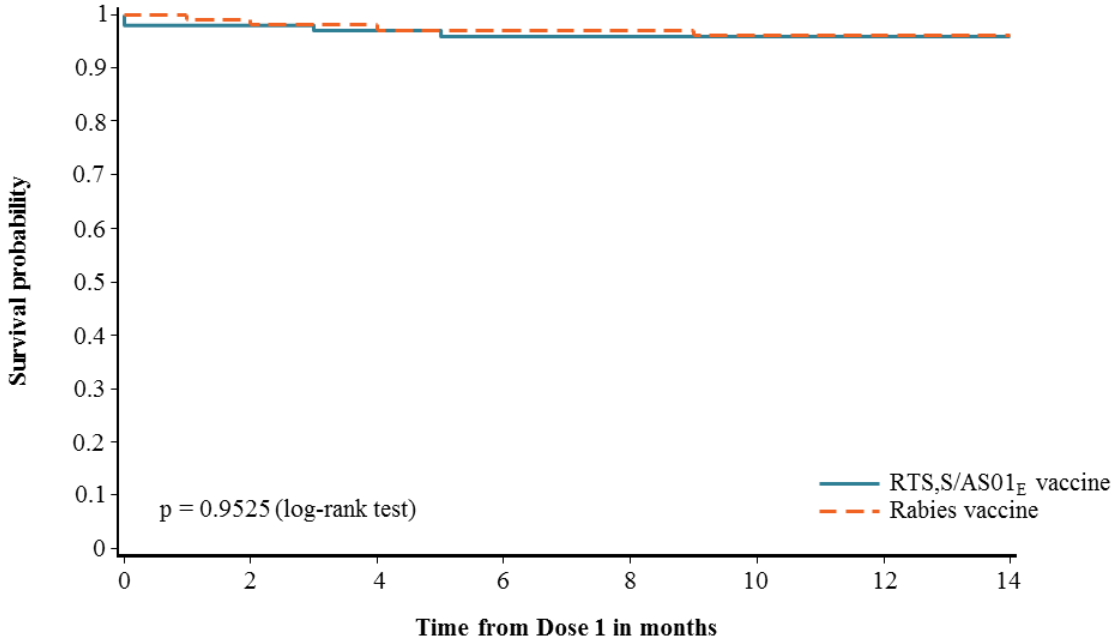
Supplementary tables and figures

Supplement Figure 1: Study design diagram



=vaccine administration. =blood sample. *Blood samples collected for safety assessment. $Blood samples collected for HIV disease progression assessment. #Blood samples collected for immunogenicity assessment. D=day. M=month.

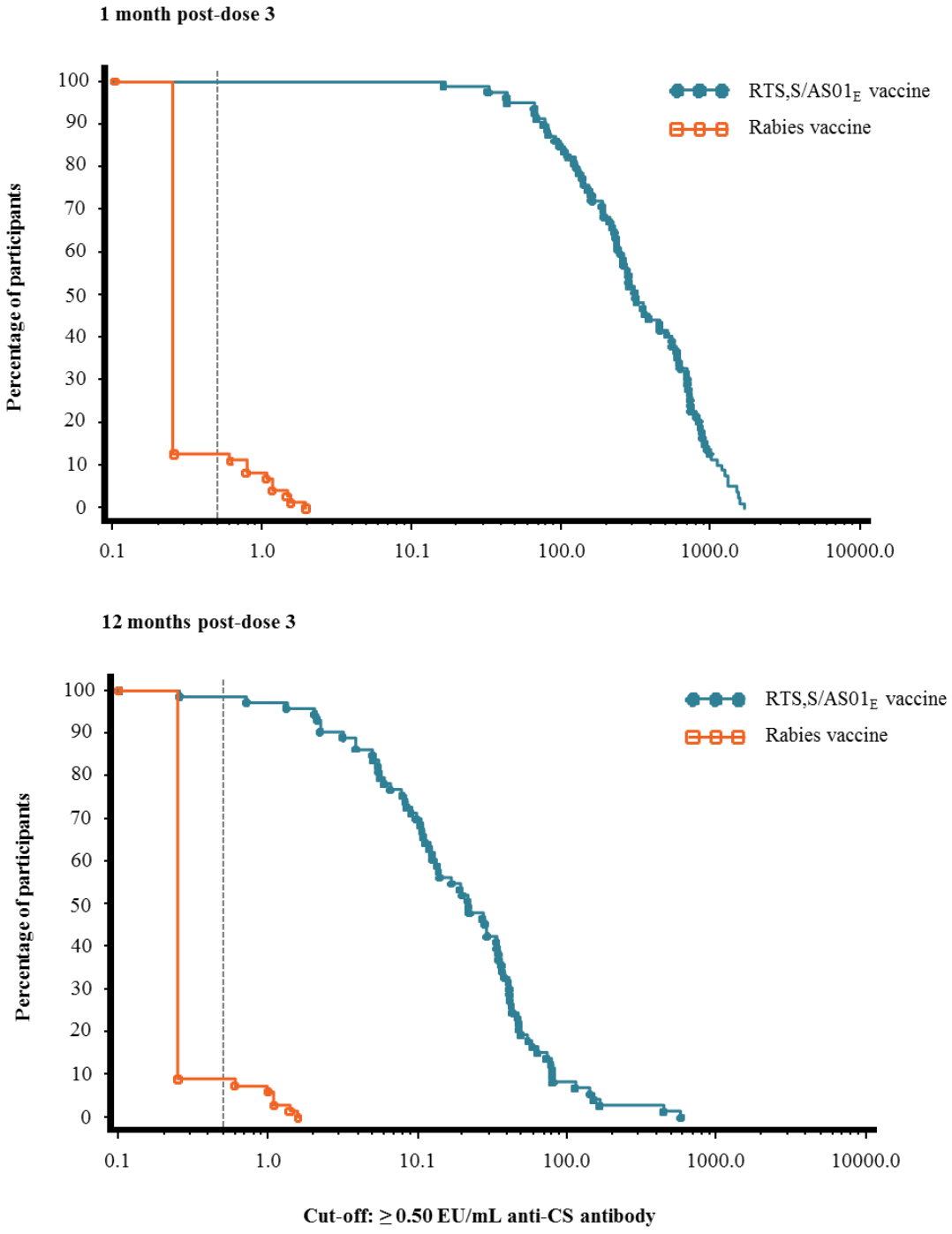
Supplement Figure 2: Survival curves



Number at risk

RTS,S/AS01$_E$ vaccine	99	95	91	89	89	89	88	37
Rabies vaccine	101	98	97	94	94	92	91	33

Supplement Figure 3: Reverse cumulative distribution curves for anti-CS antibody titres at 1 and 12 months post-dose 3 (ATP population for immunogenicity)



Anti-CS=anti-circumsporozoite; ATP=according-to-protocol; EU=enzyme-linked immunosorbent assay unit.

Supplement Table 1: Blood testing ranges

Category	Normal range	Toxicity grading scale			
		Grade 1	Grade 2	Grade 3	Grade 4
Haemoglobin	≥8·0 g/dL	<8·0 g/dL	<6·0 g/dL	<5·0 g/dL	<5·0 g/dL & clinical signs of heart failure
Total white cell count†	≥4·0 x 10^3 /μL <17 x 10^3 /μL	2·5 to 4·0 x 10^3 /μL	1·5 to 2·4 x 10^3 /μL	1·0 to 1·4 x 10^3 /μL	<1·0 x 10^3 /μL
Platelets†	≥100 x 10^3 /μL	50 to 99 x 10^3 /μL	25 to 49 x 10^3 /μL	<25 x 10^3 /μL	<25 x 10^3 /μL & clinical signs of bleeding
ALT*	≤60 IU/L	1·1 to 2·5 x ULN	2·6 to 5·0 x ULN	5·1 to 10·0 x ULN	>10·0 x ULN
Creatinine*	≤60 μmol/L (or 0·6 mg/dL)	1·1 to 1·5 x ULN	1·6 to 3·0 x ULN	3·1 to 6·0 x ULN	>6·0 ULN or requires dialysis

†Grading scale adapted from Division of AIDS table for grading severity of adult and pediatric adverse events December 2004
*Grading scale adapted from WHO Toxicity Grading Scale for Determining Severity of Adverse Events, February 2003.
ALT=alanine aminotransferase; ULN=upper limit of normal. LLN=lower limit of normal.

Supplement Table 2: Case definitions for clinical and severe malaria

Severity	Category	Parameters
Clinical Malaria	Primary case definition	– *P. falciparum >2500 parasites per μL* – *presence of fever (axillary temperature ≥ 37.5°C) at the time of presentation* – *occurring in a child who is unwell and brought for treatment to a healthcare facility*
	Secondary case definition	– *P. falciparum* >0 parasites per μL – *presence of fever (axillary temperature ≥ 37.5°C) at the time of presentation or history of fever within 24 hours of presentation*
Severe Malaria	Primary case definition 1	– *P. falciparum* >2500 parasites per μL – and with one or more marker of disease severity – and without a diagnosis of co-morbidity
	Secondary case definition 1	– *P. falciparum* >2500 parasites per μL – and with one or more marker of disease severity
	Secondary case definition 2	– *P. falciparum* >0 parasites per μL – and with one or more marker of disease severity – and without a diagnosis of co-morbidity
	Secondary case definition 3	– *P. falciparum* >0 parasites per μL – and with one or more marker of disease severity

Markers of disease severity are: prostration, respiratory distress, Blantyre score ≤2, seizures 2 or more, hypoglycaemia <2·2 mmol/L, acidosis BE 10·0 mmol/L, lactate ≥5·0 mmol/L, anaemia <5·0 g/dL.
Comorbidities are: radiographically proven pneumonia, meningitis on cerebrospinal fluid examination, positive blood culture, gastroenteritis w dehydration.

Supplement Table 3: Serious adverse events during the 30-day post-vaccination periods in children 6 weeks to 17 months at enrolment (intention-to-treat population)

Unsolicited adverse event	RTS,S/AS01 vaccine N=99		Rabies vaccine N=101	
	no. of children	% (95% CI)	no. of children	% (95% CI)
All children				
At least one unsolicited AE	20	20·2 (12·8–29·5)	12	11·9 (6·3–19·8)
At least one unsolicited AE excluding malaria	20	20·2 (12·8–29·5)	12	11·9 (6·3–19·8)
Events reported*				
Blood and lymphatic system disorders				
Anaemia	1	1·0 (0·0–5·5)	1	1·0 (0·0–5·4)
Hepatobiliary disorders				
Hepatitis	1	1·0 (0·0–5·5)	0	0·0 (0·0–3·6)
Infections and infestations				
Amoebiasis	0	0·0 (0·0–3·7)	1	1·0 (0·0–5·4)
Bronchiolitis	0	0·0 (0·0–3·7)	1	1·0 (0·0–5·4)
Gastroenteritis	8	8·1 (3·6–15·3)	7	6·9 (2·8–13·8)
Malaria	2	2·0 (0·2–7·1)	2	2·0 (0·2–7·0)
Measles	0	0·0 (0·0–3·7)	1	1·0 (0·0–5·4)
Meningitis Haemophilus	0	0·0 (0·0–3·7)	1	1·0 (0·0–5·4)
Oral candidiasis	1	1·0 (0·0–5·5)	2	2 (0·2–7·0)
Otitis media	0	0·0 (0·0–3·7)	1	1 (0·0–5·4)
Pneumococcal sepsis	0	0·0 (0·0–3·7)	1	1 (0·0–5·4)
Pneumocystis jiroveci pneumonia	1	1·0 (0·0–5·5)	0	0 (0·0–3·6)
Pneumonia	13	13·1 (7·2–21·4)	5	5 (1·6–11·2)
Salmonella sepsis	4	4·0 (1·1–10·0)	2	2 (0·2–7·0)
Sepsis (10040047)	0	0·0 (0·0–3·7)	1	1·0 (0·0–5·4)
Tuberculosis (10044755)	1	1·0 (0·0–5·5)	0	0·0 (0·0–3·6)
Urinary tract infection (10046571)	1	1·0 (0·0–5·5)	0	0·0 (0·0–3·6)
Viral infection (10047461)	0	0·0 (0·0–3·7)	1	1·0 (0·0–5·4)
Metabolism and nutrition disorders				
Malnutrition	1	1·0 (0·0–5·5)	1	1·0 (0·0–5·4)
Nervous system disorders				
Febrile convulsion	6	6·1 (2·3–12·7)	3	3·0 (0·6–8·4)

SAE=Serious adverse event. N=number of children with at least one administered dose. CI=confidence interval. *Events are listed according to the preferred terms in the Medical Dictionary for Regulatory Activities.

Supplement Table 4: Unsolicited adverse events during the 30-day post-vaccination periods in children 6 weeks to 17 months at enrolment (intention-to-treat population)

Unsolicited adverse event	RTS,S/AS01 vaccine N=99		Rabies vaccine N=101	
	no. of children	% (95% CI)	no. of children	% (95% CI)
All children				
At least one unsolicited AE	98	99·0 (94·5–100)	100	99·0 (94·6–100)
At least one unsolicited AE excluding malaria	98	99·0 (94·5–100)	100	99·0 (94·6–100)
At least one grade 3 unsolicited AE	14	14·1 (8·0–22·6)	11	10·9 (5·6–18·7)
At least one vaccine-related unsolicited AE	4	4·0 (1·1–10·0)	1	1·0 (0·0–5·4)
Events with an incidence ≥5%*				
Blood and lymphatic system disorders				
Anaemia	17	17·2 (10·3–26·1)	18	17·8 (10·9–26·7)
Eye disorders				
Conjunctivitis	13	13·1 (7·2–21·4)	12	11·9 (6·3–19·8)
Gastrointestinal disorders				
Enteritis	26	26·3 (17·9–36·1)	27	26·7 (18·4–36·5)
Vomiting	5	5·1 (1·7–11·4)	6	5·9 (2·2–12·5)
General disorders and administration site conditions				
Pyrexia	7	7·1 (2·9–14·0)	9	8·9 (4·2–16·2)
Infections and infestations				
Body tinea	6	6·1 (2·3–12·7)	3	3·0 (0·6–8·4)
Gastroenteritis	43	43·4 (33·5–53·8)	43	42·6 (32·8–52·8)
Impetigo	9	9·1 (4·2–16·6)	7	6·9 (2·8–13·8)
Malaria	22	22·2 (14·5–31·7)	22	21·8 (14·2–31·1)
Oral candidiasis	12	12·1 (6·4–20·2)	19	18·8 (11·7–27·8)
Otitis media	14	14·1 (8·0–22·6)	15	14·9 (8·6–23·3)
Pneumonia	33	33·3 (24·2–43·5)	24	23·8 (15·9–33·3)
Rhinitis	25	25·3 (17·1–35·0)	18	17·8 (10·9–26·7)
Upper respiratory tract infection	74	74·7 (65·0–82·9)	79	78·2 (68·9–85·8)
Metabolism and nutrition disorders				
Malnutrition	3	3·0 (0·6–8·6)	7	6·9 (2·8–13·8)
Nervous system disorders				
Febrile convulsion	6	6·1 (2·3–12·7)	3	3·0 (0·6–8·4)
Respiratory, thoracic and mediastinal disorders				
Bronchial hyperreactivity	8	8·1 (3·6–15·3)	14	13·9 (7·8–22·2)
Cough	6	6·1 (2·3–12·7)	3	3·0 (0·6–8·4)

Skin and subcutaneous tissue disorders				
Dermatitis diaper	2	2·0 (0·2–7·1)	5	5·0 (1·6–11·2)
Eczema	19	19·2 (12·0–28·3)	22	21·8 (14·2–31·1)
Rash	5	5·1 (1·7–11·4)	9	8·9 (4·2–16·2)
Rash papular	7	7·1 (2·9–14·0)	10	9·9 (4·9–17·5)
Rash pruritic	5	5·1 (1·7–11·4)	9	8·9 (4·2–16·2)

AE=adverse event. N=number of children with at least one administered dose. CI=confidence interval. *Events are listed according to the preferred terms in the Medical Dictionary for Regulatory Activities.

Supplement Table 5: ART and CTX status of children by time point (intention-to-treat population)

Characteristic	Parameter or category	RTS,S/AS01 vaccine N=99	Rabies vaccine N=101
ART duration;			
Up to dose 1	No. of children on treatment at dose 1	73	73
	Median no of days on treatment at dose 1 (SD)	75·00 (105·64)	49·00 (86·25)
ART duration [Category]; n (%)			
Up to dose 1	On treatment for <30 days	23 (23·2)	23 (22·8)
	On treatment for ≥30 days	50 (50·5)	50 (49·5)
	Off treatment	26 (26·3)	28 (27·7)
ART status; n (%)			
At dose 1	On treatment	73 (73·7)	73 (72·3)
	Off treatment	26 (26·3)	28 (27·7)
1M post-dose 3	On treatment	89 (96·7)	94 (97·9)
	Off treatment	3 (3·3)	2 (2·1)
6M post-dose 3	On treatment	86 (100)	91 (100)
	Off treatment	0 (0·0)	0 (0·0)
12M post-dose 3	On treatment	87 (100)	90 (100)
	Off treatment	0 (0·0)	0 (0·0)
CTX status; n (%)			
At dose 1	On treatment	92 (92·9)	92 (91·1)
	Off treatment	7 (7·1)	9 (8·9)
1M post-dose 3	On treatment	87 (94·6)	88 (91·7)
	Off treatment	5 (5·4)	8 (8·3)
6M post-dose 3	On treatment	83 (96·5)	85 (93·4)
	Off treatment	3 (3·5)	6 (6·6)
12M post-dose 3	On treatment	85 (97·7)	84 (93·3)
	Off treatment	2 (2·3)	6 (6·7)

ART=antiretroviral therapy. N=number of children. n (%)=number (percentage) of children in a given category. SD=standard deviation. CTX=co-trimoxazole.

Supplement Table 6: HIV viral load by study sites (intention-to-treat population)

Variable	Study site	Category	RTS,S/AS01 vaccine N=59/40	Rabies vaccine N=64/37
HIV viral load [copies/mL]; median (Q1–Q3)				
Screening	Kisumu		155000 (7490–750000)	165000 (4850–750000)
	Siaya		115500 (6455–532500)	157000 (3630–750000)
1M post-dose 3	Kisumu		11500 (0–457000)	1540 (0–167000)
	Siaya		1140 (0–54900)	0 (0–62100)
6M post-dose 3	Kisumu		8455 (0–182000)	400 (0–245000)
	Siaya		1815 (0–133500)	0 (0–11246)
12M post-dose 3	Kisumu		2150 (400–175000)	400 (0–108000)
	Siaya		0 (0–47600)	485 (0–79900)
HIV viral load; n (%)				
Screening	Kisumu	Detectable	50 (84·7%)	58 (90·6%)
		Not detectable	9 (15·3%)	6 (9·4%)
	Siaya	Detectable	34 (85·0%)	29 (78·4%)
		Not detectable	6 (15·0%)	8 (21·6%)
1M post-dose 3	Kisumu	Detectable	37 (68·5%)	35 (57·4%)
		Not detectable	17 (31·5%)	26 (42·6%)
	Siaya	Detectable	23 (60·5%)	16 (45·7%)
		Not detectable	15 (39·5%)	19 (54·3%)
6M post-dose 3	Kisumu	Detectable	31 (62·0%)	39 (66·1%)
		Not detectable	19 (38·0%)	20 (33·9%)
	Siaya	Detectable	21 (58·3%)	12 (37·5%)
		Not detectable	15 (41·7%)	20 (62·5%)
12M post-dose 3	Kisumu	Detectable	44 (89·8%)	43 (72·9%)
		Not detectable	5 (10·2%)	16 (27·1%)
	Siaya	Detectable	18 (48·6%)	16 (51·6%)
		Not detectable	19 (51·4%)	15 (48·4%)

HIV=human immunodeficiency virus. Q1 and Q3 represent interquartile ranges. n (%) =number (percentage) of children in a given category. N=number of children at KEMRI/WRAIR, Kisumu/KEMRI/CDC, Siaya sites. M=month(s).

Supplement Table 7: Exploratory models on HIV disease progression: changes from baseline model results of HIV viral load at different time points following dose 3 administration (intention-to-treat population)

Parameter	1M post-dose 3		6M post-dose 3		12M post-dose3	
	Parameter estimate (SE)	P-value*	Parameter estimate (SE)	P-value*	Parameter estimate (SE)	P-value*
Number of Observations	176	NA	165	NA	164	NA
Intercept	1·119 (2·124)	0·5984	0·161 (2·35)	0·9453	-0·129 (2·135)	0·9516
Baseline HIV viral load [Log10]	0·601 (0·117)	<·0001	0·355 (0·104)	0·0006	0·277 (0·086)	0·0013
RTS,S/AS01 vaccine vs. Rabies vaccine	0·52 (0·342)	0·1278	0·188 (0·339)	0·5782	0·132 (0·293)	0·6530
Age [months]	-0·092 (0·045)	0·0439	0·005 (0·045)	0·9042	0·005 (0·039)	0·8935
CD4 percentage baseline	-0·024 (0·024)	0·3089	-0·045 (0·024)	0·0566	-0·009 (0·02)	0·6385
Height-for-age z-score at baseline	-0·728 (0·248)	0·0034	-0·291 (0·228)	0·2017	-0·284 (0·187)	0·1277
Weight-for-age z-score at baseline	0·514 (0·349)	0·1412	0·328 (0·344)	0·3400	0·27 (0·295)	0·3590
MUAC z-score at baseline	-0·087 (0·262)	0·7390	-0·042 (0·256)	0·8707	-0·05 (0·224)	0·8246
Haemoglobin at baseline	0·076 (0·144)	0·5965	0·134 (0·142)	0·3455	0·151 (0·124)	0·2241
Male vs. female	-0·499 (0·349)	0·1522	-0·109 (0·344)	0·7511	0·013 (0·297)	0·9653
Siaya vs. Kombewa	-0·752 (0·37)	0·0423	-1·011 (0·382)	0·0082	-0·892 (0·337)	0·0081
ART use prior to dose 1 [duration, months]	0·192 (0·066)	0·0036	0·068 (0·064)	0·2895	0·063 (0·054)	0·2434
ART use from dose 1 to specified number of months post-dose 3 [duration, months]	-0·105 (0·246)	0·6704	0·113 (0·137)	0·4085	0·069 (0·079)	0·3797
CTX use at dose 1 [On treatment vs. Off treatment]	0·153 (0·761)	0·8406	2·375 (0·879)	0·0069	1·548 (0·752)	0·0395
CTX use from dose 1 to specified number of months post-dose 3 [duration, months]	-0·137 (0·299)	0·6461	-0·212 (0·114)	0·0632	-0·104 (0·056)	0·0615

*P-value is from censored linear regression (Tobit model). HIV=human immunodeficiency virus. M=month. SE=standard error. AIC=Akaike information criterion. MUAC=middle upper arm circumference. NA=not applicable. vs.=versus. ART=antiretroviral therapy. CTX=co-trimoxazole.

Supplement Table 8: Exploratory models on HIV disease progression: changes from baseline model results of HIV viral load at different time points following dose 3 administration, including test for interaction between vaccine assignment and ART use at dose 1 (intention-to-treat population)

Parameter	1M post-dose 3		6M post-dose 3		12M post-dose 3	
	Parameter estimate (SE)	P-value*	Parameter estimate (SE)	P-value*	Parameter estimate (SE)	P-value*
Number of Observations	176	NA	165	NA	164	NA
Intercept	1·186 (2·137)	0·5789	0·161 (2·355)	0·9456	-0·067 (2·14)	0·9751
Baseline HIV viral load [Log10]	0·601 (0·117)	<·0001	0·355 (0·104)	0·0006	0·278 (0·086)	0·0012
RTS,S/AS01 vaccine vs. Rabies vaccine	0·443 (0·433)	0·3063	0·19 (0·444)	0·6687	0·022 (0·394)	0·9561
Age [months]	-0·092 (0·045)	0·0433	0·005 (0·045)	0·9047	0·006 (0·039)	0·8859
CD4 percentage baseline	-0·026 (0·024)	0·2911	-0·045 (0·024)	0·0602	-0·0011 (0·02)	0·5872
Height-for-age z-score at baseline	-0·729 (0·248)	0·0033	-0·291 (0·228)	0·2019	-0·288 (0·187)	0·1235
Weight-for-age z-score at baseline	0·519 (0·35)	0·1378	0·328 (0·345)	0·3421	0·284 (0·297)	0·3384
MUAC z-score at baseline	-0·086 (0·262)	0·7426	-0·042 (0·256)	0·8707	-0·051 (0·224)	0·8207
Haemoglobin at baseline	0·079 (0·144)	0·5851	0·134 (0·142)	0·3465	0·154 (0·125)	0·2155
Male vs. female	-0·509 (0·351)	0·1462	-0·109 (0·347)	0·7540	-0·002 (0·299)	0·9953
Siaya vs. Kombewa	-0·745 (0·371)	0·0449	-1·011 (0·386)	0·0088	-0·871 (0·34)	0·0104
ART use prior to dose 1 [duration, months]	0·175 (0·088)	0·0473	0·068 (0·088)	0·4368	0·041 (0·075)	0·5829
ART use from dose 1 to specified number of months post-dose 3 [duration, months]	-0·108 (0·246)	0·6616	0·113 (0·137)	0·4086	0·07 (0·078)	0·3719
CTX use at dose 1 [On treatment vs. Off treatment]	0·138 (0·763)	0·8561	2·375 (0·889)	0·0076	1·506 (0·758)	0·0469
CTX use from dose 1 to specified number of months post-dose 3 [duration, months]	-0·13 (0·3)	0·6648	-0·212 (0·116)	0·0675	-0·101 (0·056)	0·0708
Interaction RTS,S/AS01E vaccine vs. Rabies vaccine x ART use prior to dose 1 [duration, months]	0·033 (0·113)	0·7728	-0·001 (0·111)	0·9948	0·04 (0·095)	0·6759

*P-value is from censored linear regression (Tobit model). HIV=human immunodeficiency virus. M=month. SE=standard error. AIC=Akaike information criterion. MUAC=middle upper arm circumference. NA=not applicable. vs.=versus. ART=antiretroviral therapy. CTX=co-trimoxazole.

Supplement Table 9: Seroprotection rates and GMTs for anti-HBs antibodies (ATP population for immunogenicity)

Groups	Time point	N	≥ 6·2 mIU/mL		≥ 10 mIU/mL		≥ 100 mIU/mL		GMT
			n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	value (95% CI)
RTS,S/AS01 vaccine	Screening	77	47	61·0 (49·2–72·0)	44	57·1 (45·4–68·4)	22	28·6 (18·8–40·0)	24·1 (15·2–38·1)
	1M post-dose 3	74	74	100 (95·1–100)	74	100 (95·1–100)	74	100 (95·1–100)	13637·6 (9579·7–19414·5)
	12M post-dose 3	70	70	100 (94·9–100)	70	100 (94·9–100)	68	97·1 (90·1–99·7)	2294·8 (1678·2–3138·0)
Rabies vaccine	Screening	73	42	57·5 (45·4–69·0)	40	54·8 (42·7–66·5)	15	20·5 (12·0–31·6)	19·2 (12·1–30·6)
	1M post-dose 3	65	39	60·0 (47·1–72·0)	34	52·3 (39·5–64·9)	15	23·1 (13·5–35·2)	19·9 (12·4–31·9)
	12M post-dose 3	64	31	48·4 (35·8–61·3)	25	39·1 (27·1–52·1)	9	14·1 (6·6–25·0)	11·8 (7·7–18·1)

ATP=according-to-protocol. GMT=geometric mean antibody titre. Anti-HBs=antibody to the hepatitis B surface antigen. N=number of children with available results. mIU/mL=milli international unit/milliliter. n/%=number/percentage of children with titre equal to or above 6·2 mIU/mL, 10 mIU/mL and 100 mIU/mL. CI=confidence interval. M=month(s).

Supplement Table 10: Efficacy of the RTS,S/AS01 vaccine against clinical malaria in children enrolled at 6 weeks to 17 months of age by primary case definition

Clinical malaria (primary case definition*)	RTS,S/AS01 vaccine			Rabies vaccine			Vaccine efficacy	
	no. of children	n	Incidence person-yr	no. of children	n	Incidence person-yr	% (95% CI)	P-value
ATP population for efficacy (follow-up from 14D to 12M post-dose 3)								
First or only episode	87	24	0·343	93	30	0·427	30·909 (-18·751–59·802)	0·1809
All episodes	87	44	0·541	93	76	0·886	37·2 (-26·5–68·8)	0·1919
Intention-to-treat population (follow-up from dose 1 to 14M post-dose 1)								
First or only episode	99	30	0·350	101	35	0·410	20·063 (-30·313–50·965)	0·3691
All episodes	99	57	0·551	101	90	0·838	29·6 (-31·8–62·4)	0·2711

*The primary case definition of clinical malaria was an illness in a child brought to a study facility with an axillary temperature of ≥37·5°C and *P. falciparum* asexual parasitaemia >2500 parasites/µL. n=number of children reporting at least one event in each group for first or only episode of clinical malaria and number of episodes included in each group for all episodes of clinical malaria. yr=year. CI=confidence interval. ATP=according-to-protocol. D=days. M=months.

Supplement Table 11: Efficacy of the RTS,S/AS01 vaccine against clinical malaria in children enrolled at 6 weeks to 17 months of age by secondary case definitions

Category	RTS,S/AS01 vaccine			Rabies vaccine			Vaccine efficacy	
	no. of children	n	Incidence person-yr	no. of children	n	Incidence person-yr	% (95% CI)	P-value
Clinical malaria (secondary case definition*)								
ATP for efficacy (follow-up from 14D to 12M post-dose 3)								
First or only episode	87	31	0·470	93	40	0·624	33·839 (-6·250–58·802)	0·0874
All episodes	87	65	0·807	93	105	1·239	37·5 (-13·1–65·4)	0·1197
Intention-to-treat population (follow-up from dose 1 to 14M post-dose 1)								
First or only episode	99	43	0·588	101	48	0·650	18·484 (-23·387–46·147)	0·3339
All episodes	99	91	0·890	101	133	1·258	28·7 (-17·0–56·6)	0·1797
Clinical malaria (secondary case definition 2)**								
ATP for efficacy (follow-up from 14D to 12M post-dose 3)								
First or only episode	87	23	0·326	93	29	0·408	29·826 (-21·755–59·555)	0·2077
All episodes	87	42	0·516	93	71	0·826	36·6 (-28·2–68·7)	0·2030
Intention-to-treat population (follow-up from dose 1 to 14M post-dose 1)								
First or only episode	99	30	0·349	101	33	0·379	13·498 (-41·951–47·287)	0·5661
All episodes	99	54	0·521	101	84	0·781	27·6 (-36·2–61·5)	0·3153
Clinical malaria (secondary case definition 3*)**								
ATP for efficacy (follow-up period from 14D to 12M post-dose 3)								
First or only episode	87	19	0·260	93	26	0·357	36·449 (-15·254–64·958)	0·1356
All episodes	87	33	0·404	93	59	0·682	40·4 (-25·1–71·6)	0·1701
Intention-to-treat population (follow-up from dose 1 to 14M post-dose 1)								
First or only episode	99	26	0·289	101	30	0·337	21·853 (-32·362–53·862)	0·3591
All episodes	99	43	0·413	101	70	0·647	29·5 (-35·1–63·2)	0·2909

*The secondary case definition of clinical malaria was an illness in a child brought to a study facility with a measured temperature of ≥37·5°C or reported fever within the last 24 hours and *P. falciparum* asexual parasitaemia >0 parasites/μL.
**The secondary case definition 2 of clinical malaria was an illness in a child brought to a study facility with a measured temperature of ≥37·5°C and *P. falciparum* asexual parasitaemia >5000 parasites/μL.
***The secondary case definition 3 of clinical malaria was an illness in a child brought to a study facility with a measured temperature of ≥37·5°C *P. falciparum* asexual parasitaemia >20000 parasites/μL.
n=number of children reporting at least one event in each group for first or only episode of clinical malaria and number of episodes included in each group for all episodes of clinical malaria. yr=year. CI=confidence interval. ATP=according-to-protocol. D=days. M=months.

Supplement Table 12: Number of episodes of severe malaria (primary case definition*) (all episodes) (intention-to-treat population)

Groups	Time point	N	n	%
RTS,S/AS01 vaccine	12M post-dose 3	87	1	1·1
Rabies vaccine	12M post-dose 3	93	8	8·6

*The primary case definition of severe malaria was an illness in a child brought to a study facility with *P. falciparum* >2500 parasites/μL, and with one or more marker of disease severity, and without a diagnosis of co-morbidity. N=number of children. n/%=number/percentage of children with number of episodes of malaria within risk period (14 days following episode). M=months.

Supplement Table 13: Growth progression (intention-to-treat population)

Variable	RTS,S/AS01 vaccine N=99	Rabies vaccine N=101
Height-for-age z-score; mean ± SD		
Screening	-1·67 ± 1·20	-1·98 ± 1·37
1M post-dose 3	-1·91 ± 1·14	-2·12 ± 1·16
12M post-dose 3	-1·74 ± 1·19	-2·26 ± 1·18
Weight-for-age z-score; mean ± SD		
Screening	-1·38 ± 1·13	-1·67 ± 1·19
1M post-dose 3	-1·32 ± 1·10	-1·55 ± 1·09
12M post-dose 3	-1·10 ± 1·14	-1·47 ± 1·02
MUAC z-score; mean ± SD		
Screening	-0·65 ± 1·13	-0·90 ± 1·19
1M post-dose 3	-0·39 ± 1·03	-0·65 ± 1·04
12M post-dose 3	-0·29 ± 1·13	-0·51 ± 0·93

N=number of children. SD=standard deviation. M=month(s). MUAC=middle upper arm circumference.