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Question: Should a malaria vaccine be provided to reduce malaria disease burden in children ≥ 5 months of age living in regions with endemic malaria transmission?

Population: Children ≥ 5 months of age

Intervention: Malaria vaccination

Comparison: Malaria prevention interventions currently in place without malaria vaccination

Setting: regions with endemic low, moderate, or high malaria transmission

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
CLINICAL MALARIA **(Impact, critical outcome)**	**Age-based administration** (year-round delivery of all 4 doses based on child's age)								
	RTS,S/AS01 versus control[1]	Ph 3 randomised trial; 2009-2014 (**month 0 to end of study; median 48 months' follow-up)**	N=2976; 6616 episodes	N=2974; 9585 episodes	VE: 36.3% (31.8 to 40.5)[2]	Study population		⊕⊕⊕⊕ HIGH	*RTS,S/AS01 vaccination reduces clinical malaria episodes*
							1774 fewer cases per 1000 children (1387 fewer to 2186 fewer)[3]		
						Low transmission[4]			
							205-303 fewer cases per 1000 children		
						Moderate transmission[5]			

[1] **5950 total participants:** four-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20; Control group received comparator vaccine at months 0, 1, 2, and 20

[2] **Modified ITT analysis VE** (participants receiving at least 1 vaccine dose, with follow-up from dose 1)**;** PP analysis VE: 39% (34.3% to 43.3%)

[3] In children aged 5-17 months, 1363 cases of clinical malaria were averted per 1000 children (95% CI 995-1797) in the R3C group

[4] RTS,S/AS01 Phase 3 low transmission sites: Kilifi, Kenya and Korogwe, Tanzania

[5] RTS,S/AS01 Phase 3 moderate transmission sites Lambarene, Gabon; Bagamoyo, Tanzania; Lilongwe, Malawi; Manhiça, Mozambique

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
CLINICAL MALARIA **(Impact, critical outcome)**							236-685 fewer cases per 1000 children		
						High transmission[6]			
							2722-6565 fewer cases per 1000 children		
	RTS,S/AS01 versus control[7]	Ph 2b randomised trial; 2017-2018 (**month 0 – month 20**)	N=298; 341 episodes	N=293; 476 episodes	VE: 39% (23 to 51)[8]	476 per 406 PYAR	457 fewer cases per 1000 PYAR (598 fewer to 270 fewer)	⊕⊕⊕◯ MODERATE Due to imprecision[9]	*RTS,S/AS01 vaccination probably reduces clinical malaria episodes*
	R21/Matrix-M versus control[10]	Ph 3 randomised trial; 2019-ongoing; (**month 0 – month 14; 12 months follow-up post-dose 3**)[11]	315/1636 (19.3%); 1840 PYAR	406/815 (49.8%); 911 PYAR	VE: 61% (53 to 67)[12]	Study population		⊕⊕⊕◯ MODERATE Due to indirectness[13]	*R21/Matrix-M vaccination probably reduces clinical malaria episodes*
						406 per 911 PYAR	272 fewer cases per 1000 PYAR (299 fewer to 236 fewer)		
						Low to Moderate transmission[14]			

[6] RTS,S/AS01 Phase 3 high transmission sites: Siaya, Kenya; Nanoro, Burkina Faso; Kintampo, Burkina Faso; Kombewa, Kenya; Agogo, Ghana

[7] **1609 total participants**: 4 dose groups (only group 1 was used): Group 1 [n=322]: RTS,S/AS01 – 3 standard 0.5 mL doses at months 0, 1 and 2, followed by standard dose at month 20, Group 2 [n=322]: RTS,S/AS01 – 3 standard 0.5 mL doses at months 0, 1 and 2, followed by standard doses at months 14, 26 and 38, Group 3 [n=322]: RTS,S/AS01 – 2 standard 0.5 mL doses at months 0 and 1, followed by fractional doses (0.1 mL) at months 2, 14, 26 and 38, Group 4 [n=322]: RTS,S/AS01 – 2 standard 0.5 mL doses at months 0 and 1, followed by fractional doses (0.1 mL) at months 7, 20 and 32; Control received comparator vaccine at 12 months.: Group 5 [n=321]: rabies vaccine (M012 schedule)

[8] **Modified ITT analysis VE**; (participants receiving at least one vaccine dose with follow-up beginning from dose 1)

[9] Downgraded one level due to imprecision: confidence interval crosses threshold for a worthwhile effect (30%)

[10] **2400 total participants (age-based administration)**: Participants aged 5-36 months were randomised 2:1 to receive vaccination with R21 adjuvanted with Matrix-M, or a control vaccination (a licensed rabies vaccine). Group 1 [n=1600]: 3 doses R21 adjuvanted with Matrix-M standard vaccination regime; Control group: Group 2 [n=800]: 3 doses rabies vaccine (Rabivax-S). 4800 total participants across seasonal and age-based strategies.

[11] Estimated study completion 2024: https://classic.clinicaltrials.gov/ct2/show/NCT04704830

[12] **Modified ITT analysis** (participants receiving at least one vaccine dose with follow-up beginning from dose 3)

[13] Downgraded one level for indirectness due to lack of data in high transmission settings

[14] Dande, Burkina Faso (moderate); Bagamoyo, Tanzania (low to moderate); Kilifi, Kenya (moderate)

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
CLINICAL MALARIA **(Impact, critical outcome)**						300-567 per 1000 PYAR	162-369 fewer cases per 1000 PYAR		
						High transmission			
						No Phase 3 trial sites with age-based administration in high transmission areas			
	Seasonal administration (seasonally timed delivery of all 4 or 5 doses; first 3 doses provided monthly prior to start of peak transmission season; subsequent doses provided annually)								
	RTS,S/AS01 alone versus SMC alone[15]	Ph 3b randomised trial 2017 – 2020; **3 years follow-up**	278.2 (264.6 to 292.4)/1000 PYAR; 1540 events over 5535.7 PYAR	304.8 (290.5 to 319.8)/1000 PYAR; 1661 events over 5449.9 PYAR	HR 0.92 (99%CI 0.82 to 1.04)[16]	1661/5450 PYAR	21 fewer cases per 1000 PYAR (47 fewer to 10 more)[17]	⊕⊕⊕⊕ HIGH	*RTS,S/AS01 vaccination is non-inferior to SMC in reducing clinical malaria*
	RTS,S/AS01 + SMC combination vs SMC alone[18]	Ph 3b randomised trial 2017 – 2020; **3 years follow-up**	113.3 (104.7 to 122.5) /1000 PYAR; 624 events over 5508.0 PYAR	304.8 (290.5 to 319.8)/1000 PYAR; 1661 events over 5449.9 PYAR	PE: 62.8% (58.4% to 66.8%)[19]	1661/5450 PYAR	191 fewer cases per 1000 PYAR (204 fewer to 178 fewer)	⊕⊕⊕⊕ HIGH	*The combination of RTS,S/AS01 vaccination with SMC is superior to SMC alone in reducing clinical malaria*

[15] **3953 total participants**: Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).

[16] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1); Protective Efficacy: 7.9% (-1.0 to 16.0)

[17] Number of events averted per child: 27 fewer per 1000 (CI 95% 13 fewer — 40 fewer)

[18] **3932 total participants:** Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).

[19] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
CLINICAL MALARIA (Impact, critical outcome)	**R21/Matrix-M versus control[20]**	Ph 2b randomised trial; 2019-2021; (**12 months follow-up post dose 3)**	39/146 (27%)	106/147 (72%)	VE: 77% (67% to 84%)[21]	106/147 (720 per 1000)	555 fewer per 1000 (606 fewer to 483 fewer)	⊕⊕⊕⊕ HIGH	*R21/Matrix-M vaccination reduces clinical malaria cases*
	R21/Matrix-M versus control[22]	Ph 3 randomised trial; 2019-ongoing (**month 0-month 20; 18 months follow-up post-dose 3**)	932/1613 (57.8%); 2665 PYAR	1688/811 (208.1%); 1335 PYAR	VE: 74% (70% to 76%)[23]	Study population		⊕⊕⊕⊕ HIGH	*R21/Matrix-M vaccination reduces clinical malaria cases*
						1688/1335 PYAR	936 fewer per 1000 PYAR (961 fewer to 885 fewer)		
						Low transmission			
						No Phase 3 trial sites with seasonal administration in low transmission areas			
						Moderate to high transmission[24]			
						534 per 1000 PYAR	450 fewer cases per 1000 PYAR		
						High transmission[25]			
						1515 per 1000 PYAR	1229 fewer cases per 1000 PYAR		

[20] **450 total participants:** Two dose groups: Group 1 [n=150]: 3 doses 5 µg R21 adjuvanted with 25 mcg Matrix-M at months 0, 1 and 3 (May – August, before Malaria season), with a booster at month 12, Group 2 [n=150]**:** 3 doses 5 µg R21 adjuvanted with 50 mcg Matrix-M at months 0, 1 and 3 (May – August, before Malaria season), with a booster at month 12; Control group: Group 3 [n=150]: received 3 doses Rabivax-S rabies vaccine at months 0, 1 and 3 (May – August, before Malaria season), with a booster at month 12.

[21] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 3)

[22] **2400 total participants (seasonal administration)**: Participants aged 5-36 months were randomised 2:1 to receive vaccination with R21 adjuvanted with Matrix-M, or a control vaccination (a licensed rabies vaccine). Group 3 [n=1600]: 3 doses R21 adjuvanted with Matrix-M seasonal vaccination regime; Control group: Group 4 [n=800]: 3 doses rabies vaccine (Rabivax-S). 4800 total participants across seasonal and age-based strategies.

[23] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)

[24] Bougouni, Mali

[25] Nanoro, Burkina Faso

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
SEVERE MALARIA	**Age-based administration**								
(Impact, important outcome)	**RTS,S/AS01 versus control**[1]	Ph 3 randomised trial 2009-2014 (**month 0 to end of study; median 48 months' follow-up**)	N=2976; 116 episodes	N=2974; 171 episodes	VE: 32.2% (13.7% to 46.9%)[26]	171/2974 (57 per 1000)	19 fewer per 1000 (27 fewer to 8 fewer)	⊕⊕⊕⊕ HIGH	*RTS,S/AS01 vaccination reduces severe malaria*
	RTS,S/AS01 vaccination in implementing areas vs comparison areas[27]	pilot implementation study*; 2019-2021 (**month 0 to month 24**)	-	-	IRR 0.70 (0.54 to 0.92)[28]	-	-	⊕⊕⊕◯ MODERATE Due to imprecision[29]	*RTS,S/AS01 vaccine introduction is probably associated with a reduced incidence of hospital admissions with severe malaria.*
	RTS,S/AS01 versus control[7]	Ph 2b randomised trial 2017-2018 (**20 months follow-up**)	N = 298; 13 episodes	N = 293; 31 episodes	RR 0.44 (0.23 to 0.82)[23]	31/293 (106 per 1000)	59 fewer per 1000 (81 fewer to 19 fewer)	⊕⊕⊕◯ MODERATE Due to imprecision[30]	*RTS,S/AS01 vaccination probably reduces severe malaria*

[26] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1); PP analysis VE: 28.5% (6.3% to 45.7%)
[27] **MVPE surveillance data** Group 1: The vaccine schedule involves four doses, at 6, 7, 9 and 24 months of age in Ghana and Kenya and at 5, 6, 7 and 22 months in Malawi; Control group: Group 2: Delayed introduction (i.e., no malaria vaccine)
[28] Reduction in incidence of admission with severe malaria between implementing and comparison areas of 30% (8% to 46%)
[29] Downgraded one level for imprecision: few events and CI that includes no effect
[30] Downgraded one level for imprecision: few events and CI that includes no effect

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
SEVERE MALARIA (Impact, important outcome)	**R21/Matrix-M versus control**[10]	Ph 3 randomised trial; 2019-ongoing; (**month 0 – month 14; 12 months follow-up post-dose 3**)[11]	7/1636 (0.4%)	3/815 (0.4%)	VE: -0.11 (-3.29 to 0.71)[23]	3/815 4 per 1000	0 fewer per 1000 (3 fewer to 12 more)	⊕⊕◯◯ LOW Due to serious imprecision[31]	*Too few events and small sample size to determine an association between R21/Matrix-M vaccination and severe malaria*
	Seasonal administration								
	RTS,S/AS01 alone versus SMC alone[15]	Ph 3b randomised trial 2017-2020; **3 years' follow-up**	37 events; 6.7 (4.8 to 9.2) per 1000 PYAR	37 events; 6.8 (4.9 to 9.4) per 1000 PYAR	PE: -0.4% (-60.2% to 37.1%)[32]	6.8 per 1000	0 fewer per 1000 (2 fewer to 4 more)	⊕⊕◯◯ LOW Due to serious imprecision[33]	*There may be little or no difference between RTS,S/AS01 vaccination and SMC in reducing hospitalization with severe malaria.*
	RTS,S/AS01 + SMC combination vs SMC alone[18]	Ph 3b randomised trial 2017-2020; **3 years' follow-up**	11 events; 2.0 (1.1 to 3.6) per 1000 PYAR	37 events; 6.8 (4.9 to 9.4) per 1000 PYAR	PE: 70.5% (41.9% to 85.0%)[19]	6.8 per 1000	4.8 fewer per 1000 (3.2 fewer to 5.7 fewer)	⊕⊕⊕◯ MODERATE Due to imprecision[34]	*The combination of RTS,S/AS01 vaccination with SMC is probably superior to SMC alone in reducing hospitalization with severe malaria*

[31] Downgraded two levels due to serious imprecision: few events and a very wide confidence interval that incorporates the possibility of benefit and harm.
[32] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1); Most cases were severe malaria anaemia (vaccine: 25/37; SMC: 31/37)
[33] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm.
[34] Downgraded one level for imprecision: few events and CI that includes no effect.

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
	R21/Matrix-M versus control[22]	Ph 3 randomised trial; 2019-ongoing (**month 0-month 20; 18 months follow-up post-dose 3**)	8/1613 (0.5%)	8/811 (1%)l	VE: 50% (-33% to 81%)[23]	8/811 (10 per 1000)	5 fewer per 1000 (8 fewer to 3 more)	⊕⊕◯◯ LOW Due to serious imprecision[35]	*Too few events and small sample size to determine an association between R21/Matrix-M vaccination and severe malaria*
SEVERE MALARIA ANAEMIA (Impact, important outcome)	**Age-based administration**								
	RTS,S/AS01 versus control[1]	Ph 3 randomised trial 2009-2014 (**month 0 to end of study; median 48 months' follow-up**)	23/2976 (0.8%)	44/2974 (1.5%)	VE: 47.8% (11.6% to 69.9%)[36]	44/2974 (15 per 1000)	7 fewer per 1000 (10 fewer to 2 fewer)	⊕⊕⊕◯ MODERATE Due to imprecision[37]	*RTS,S/AS01 vaccination probably reduces severe malaria anaemia.*
	Seasonal administration								
	RTS,S/AS01 alone versus SMC alone[15]	Ph 3b randomised trial 2017 – 2020; **3 years follow-up**	25 events; 4.5 (3.1 to 6.7) per 1000 PYAR	31 events; 5.7 (4.0 to 8.1) per 1000 PYAR	PE: 18.4% (-39.3% to 52.2%)[38]	5.7 per 1000	1.17 fewer per 1000 (2.64 fewer to 0.99 more)	⊕⊕◯◯ LOW Due to serious imprecision[39]	*There may be little or no difference between RTS,S/AS01 vaccination and SMC in reducing severe malaria anaemia.*

[35] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm.
[36] Modified ITT analysis (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)
[37] Downgraded one level for imprecision: few events and CI that includes no effect.
[38] Modified ITT analysis (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)
[39] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm.

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
	RTS,S/AS01 + SMC combination vs SMC alone[18]	Ph 3b randomised trial 2017 – 2020; **3 years follow-up**	10 events; 1.8 (1.0 to 3.4) per 1000 PYAR	31 events; 5.7 (4.0 to 8.1) per 1000 PYAR	PE: 67.9% (-34.1% to 84.3%)[38]	5.7 per 1000	4 fewer per 1000 (5 fewer to 2 fewer)	⊕⊕⊕◯ MODERATE Due to imprecision[40]	*A combination of RTS,S/AS01 vaccination and SMC probably reduces severe malaria anaemia.*
	R21/Matrix-M versus control[22]	Ph 3 randomised trial; 2019-ongoing (**month 0-month 20; 18 months follow-up post-dose 3**)[11]	-	-	-	-	-	-	*Data not available*
BLOOD TRANSFUSIONS (Impact, important outcome)	**Age-based administration**								
	RTS,S/AS01 versus control[1]	Ph 3 randomised trial 2009-2014 (**month 0 to end of study; median 48 months' follow-up**)	78/2976 (2.6%)	109/2974 (3.7%)	VE 28.5% (3.5% to 47.2%)[41]	109/2974 (37 per 1000)	10 fewer per 1000 (17 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE Due to imprecision[42]	*RTS,S/AS01 vaccination probably reduces the need for blood transfusions.*
	R21/Matrix-M versus control	Ph 3 randomised trial; 2019-ongoing (month 0-month 20; 18 months follow-up post-dose 3)	-	-	-	-	-	-	*Data not available*
	Seasonal administration								

[40] Downgraded one level for imprecision: few events and CI that includes no effect.
[41] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)
[42] Downgraded one level for imprecision: few events and CI that includes no effect.

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
BLOOD TRANSFUSIONS (Impact, important outcome)	**RTS,S/AS01 alone versus SMC alone**[15]	Ph 3b randomised trial 2017 – 2020; **3 years follow-up**	21 events; 3.8 (2.5 to 5.8) per 1000 PYAR	23 events; 4.2 (2.8 to 6.4) per 1000 PYAR	PE: 8.3% (-67.6 to 49.8)[43]	4.2 per 1000	0.43 fewer per 1000 (1.75 fewer to 1.6 more)	⊕⊕◯◯ LOW Due to serious imprecision[44]	*There may be little or no difference between RTS,S/AS01 vaccination and SMC in reducing the need for blood transfusions.*
	RTS,S/AS01 + SMC combination vs SMC alone[18]	Ph 3b randomised trial 2017 – 2020; **3 years follow-up**	8 events; 1.5 (0.7 to 2.9) per 1000 PYAR	23 events; 4.2 (2.8 to 6.4) per 1000 PYAR	PE: 65.40% (22.90 to 84.50)[45]	4.2 per 1000	2.77 fewer per 1000 (1.32 fewer to 3.49 fewer)	⊕⊕◯◯ LOW Due to serious imprecision[46]	*The combination of RTS,S/AS01 vaccination with SMC may be superior to SMC alone in reducing the need for blood transfusions.*
	R21/Matrix-M versus control	Ph 3 randomised trial; 2019-ongoing (month 0-month 20; 18 months follow-up post-dose 3)	-	-	-	-	-	-	*Data not available*

[43] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)
[44] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm.
[45] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)
[46] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm.

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
ALL-CAUSE HOSPITAL ADMISSIONS (Impact, important outcome)	**Age-based administration**								
	RTS,S/AS01 versus control[1]	Ph 3 randomised trial 2009-2014 (**month 0 to end of study; median 48 months' follow-up**)	644/2976 (21.6%)	771/2974 (25.9%)	VE 16.5% (7.2 to 24.9)[47]	771/2974 (259 per 1000)	43 fewer per 1000 (65 fewer to 19 fewer)	⊕⊕⊕⊕ HIGH	*RTS,S/AS01 vaccination reduces all-cause hospital admissions*
	RTS,S/AS01 vaccination in implementing areas vs comparison areas[27]	pilot implementation study*, 2019-2021 (**month 0 to month 24**)	-	-	IRR 0.92 (0.83 to 1.03)[48]			⊕⊕⊕◯ MODERATE Due to imprecision[49]	*RTS,S/AS01 vaccine introduction probably has little or no effect on all-cause hospital admissions.*
	R21/Matrix-M versus control	Ph 3 randomised trial; 2019-ongoing **(month 0-month 14; 12 months follow-up post-dose 3)**	-	-	-	-	-		*Data not available*

[47] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)
[48] The rate ratio comparing the incidence of all-cause hospital admission between implementation and comparison areas, for this age group, was 0.92 (95%CI 0.83 to 1.03), a reduction of 8% (95%CI -3% to 17%).
[49] Downgraded one level due to imprecision: wide confidence interval that incorporates the possibility of benefit and of no effect.

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
ALL-CAUSE HOSPITAL ADMISSIONS (Impact, important outcome)	**Seasonal administration**								
	RTS,S/AS01 alone versus SMC alone[15]	Ph 3b randomised trial 2017 – 2020; **3 years follow-up**	73 events; 13.2 (10.5 to 16.6) per 1000 PYAR	60 events; 11.0 (8.6 to 14.2) per 1000 PYAR	PE -22.3% (-74.4 to 14.3)[50]	11 per 1000	2.2 more per 1000 (2 fewer to 8 more)	⊕⊕◯◯ LOW Due to serious imprecision[51]	*There may be little or no difference between RTS,S/AS01 vaccination and SMC in reducing all-cause hospital admissions.*
	RTS,S/AS01 + SMC combination vs SMC alone[18]	Ph 3b randomised trial 2017 – 2020; **3 years follow-up**	49 events; 8.9 (6.7 to 11.8) per 1000 PYAR	60 events; 11.0 (8.55 to 14.2) per 1000 PYAR	PE: 18.7 (-19.4 to 44.7)[52]	11 per 1000	2.1 fewer per 1000 (4.28 fewer to 0.8 more)	⊕⊕◯◯ LOW Due to serious imprecision[53]	*There may be little or no difference between the combination of RTS,S/AS01 vaccination with SMC and SMC alone in reducing all-cause hospital admissions.*
	R21/Matrix-M versus control	Ph 3 randomised trial; 2019-ongoing (month 0-month 20; 18 months follow-up post-dose 3)	-	-	-	-	-	-	*Data not available*

[50] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)
[51] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm.
[52] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)
[53] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm.

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
MALARIA HOSPITAL ADMISSIONS (Impact, important outcome)	**Age-based administration**								
	RTS,S/AS01 implementing vs comparison areas[27]	pilot implementation study*, 2019-2021 (**month 0 to month 24**)	-	-	IRR: 0.79 (0.68 to 0.93)[54]	-	-	⊕⊕⊕◯ MODERATE Due to imprecision[55]	*RTS,S/AS01 vaccine introduction is probably associated with reduced hospital admissions with a positive malaria test.*
	R21/Matrix-M versus control[10]	Ph 3 randomised trial; 2019-ongoing; (**month 0 – month 14; 12 months follow-up post-dose 3**)[11]	9/1636 (0.6%)	4/815 (0.5%)	VE: -8% (-250% to 67%)[56]	4/815 (5 per 1000)	0 fewer per 1000 (3 fewer to 3 more)	⊕⊕◯◯ LOW Due to serious imprecision[57]	*Too few events and small sample size to determine an association between R21/Matrix-M vaccination and malaria hospital admission.*
	Seasonal administration								
	RTS,S/AS01 alone versus SMC alone[15]	Ph 3b randomised trial 2017 – 2020; **3 years follow-up**	54 events; 9.8 (7.5 to 12.7) per 1000 PYAR	49 events; 9.0 (6.8 to 11.9) per 1000 PYAR	PE: -11.0% (-65.8% to 25.7%)[58]	9 per 1000	1 more per 1000 (2 fewer to 6 more)	⊕⊕◯◯ LOW Due to serious imprecision[59]	*There may be little or no difference between RTS,S/AS01 vaccination and SMC in reducing malaria hospital admissions.*

[54] The rate ratio comparing the incidence of hospital admission with a positive malaria test between implementation and comparison areas was 0.79 (95%CI 0.68 to 0.93), a reduction of 21% (95%CI 7% to 32%).
[55] Downgraded one level for imprecision: few events and CI that includes no effect.
[56] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)
[57] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm.
[58] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)
[59] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm.

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
	RTS,S/AS01 + SMC combination vs SMC alone[18]	Ph 3b randomised trial 2017 – 2020; **3 years follow-up**	28 events; 5.1 (35 to 7.4) per 1000 PYAR	49 events; 9.0 (6.8 to 11.9) per 1000 PYAR	PE: 43.2% (7.7% to 65.0%)[60]	9 per 1000	4 fewer per 1000 (6 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE Due to imprecision[61]	*The combination of RTS,S/AS01 vaccination with SMC probably reduces malaria hospital admissions compared with SMC alone.*
	R21/Matrix-M versus control[22]	Ph 3 randomised trial; 2019-ongoing (**month 0-month 20; 18 months follow-up post-dose 3**)	8/1613 (0.5%)	8/811 (1%)	VE: 50% (-32% to 81%)[62]	8/811 (10 per 1000)	5 fewer per 1000 (8 fewer to 3 more)	⊕⊕◯◯ LOW Due to serious imprecision[63]	*Too few events and small sample size to determine an association between R21/Matrix-M vaccination and malaria hospital admission.*
ALL-CAUSE MORTALITY (Impact, important outcome)	**Age-based administration**								
	RTS,S/AS01 (3-dose and 4-dose) versus control	Ph 3 randomised trial 2009-2014 (**month 0 to study end; median 48 months follow-up**)	R3R: 61 2976 (2.0%) + R3C: 51 2972 (1.7%)	C3C: 46 2974 (1.5%)	RR: 1.21 (0.86 to 1.71)[64]	46/2974 (15 per 1000)	3 more per 1000 (2 fewer to 11 more)	⊕⊕◯◯ LOW Due to serious imprecision[65]	*RTS,S/AS01 vaccination may result in little or no difference in all-cause mortality.*

[60] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)
[61] Downgraded one level for imprecision: few events and CI that includes no effect.
[62] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)
[63] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm.
[64] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)
[65] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm.

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
ALL-CAUSE MORTALITY (Impact, important outcome)	**RTS,S/AS01 versus control**[7]	Ph 2b randomised trial 2017-2018 (**20 months follow-up**)	1/298	0/293	Not estimable	-	-	⊕⊕◯◯ LOW Due to serious imprecision[66]	*RTS,S malaria vaccination may result in little or no difference in all-cause mortality.*
	R21/Matrix-M versus control[10]	Ph 3 randomised trial; 2019-ongoing; (**month 0 – month 14; 12 months follow-up post-dose 3**)[11]	7/1636 (0.4%)	2/815 (0.2%)	RR 1.74 (0.36 to 8.36)[67]	2/815 (2.5 per 1000)	2 more per 1000 (2 fewer to 18 more)	⊕⊕◯◯ LOW Due to serious imprecision[68]	*There were too few deaths to determine an association between R21/Matrix-M vaccination and all-cause mortality.*
	Seasonal administration								
	RTS,S/AS01 alone versus SMC alone[15]	Ph 3b randomised trial 2017 – 2020; **3 years follow-up**	27 events; 4.9 (3.3 to 7.1) per 1000 PYAR	32 events; 5.9 (4.2 to 8.3) per 1000 PYAR	PE: 15.9% (-40.3 to 49.6)[69]	5.9 per 1000	6 fewer per 1000 (23 fewer to 26 more)	⊕⊕◯◯ LOW Due to serious imprecision[70]	*RTS,S/AS01 vaccination may result in little or no difference in all-cause mortality compared with SMC alone.*

[66] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm.
[67] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)
[68] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm.
[69] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)
[70] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm.

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
ALL-CAUSE MORTALITY (Impact, important outcome)	**RTS,S/AS01 + SMC combination vs SMC alone**[18]	Ph 3b randomised trial 2017 – 2020; **3 years follow-up**	15 events; 2.7 (1.6 to 4.5) per 1000 PYAR	32 events; 5.9 (4.2 to 8.3) per 1000 PYAR	PE: 53.4% (14.0 to 74.8)[71]	5.9 per 1000	3 fewer per 1000 (4 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE Due to imprecision[72]	*The combination of RTS,S/AS01 vaccination with SMC probably reduces all-cause mortality compared with SMC alone.*
	R21/Matrix-M versus control[20]	Ph 2b randomised trial; 2019-2021; (**12 months follow-up post dose 3)**	0/146	0/147	Not estimable	-	-	⊕⊕◯◯ LOW Due to serious imprecision[73]	*Due to zero deaths and small sample size, cannot determine an association between R21/Matrix-M vaccination and all-cause mortality.*
	R21/Matrix-M versus control[22]	Ph 3 randomised trial; 2019-ongoing (**month 0 to 20; 19 months post dose 3**)	8/1613 (0.5%)	2/811 (0.2%)	RR 2.01 (0.43 to 9.43)[74]	2/811 (2.5 per 1000)	2 more per 1000 (1 fewer to 21 more)	⊕⊕◯◯ LOW Due to serious imprecision[75]	*There were too few deaths to determine impact on all-cause mortality with R21/Matrix-M vaccination.*

[71] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)
[72] Downgraded one level for imprecision: few events and CI that includes no effect.
[73] Downgraded two levels due to serious imprecision: no events reported in either group.
[74] Modified ITT analysis (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)
[75] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm.

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
SERIOUS ADVERSE EVENTS (Safety, critical outcome)	**RTS,S/AS01 versus control**	Ph 3 randomised trial; 2009-2014 (**month 0 to end of study; median 48 months' follow-up)**	R3R : 673/ 2976 (22.6%) R3C: 704/ 2972 (23.7%) Total: 1377/5948[76] (23.2%)	C3C: 784/2974 (26.4%)	0.88 (0.81 to 0.95)	784/2974 (264 per 1000)	32 fewer per 1000 (from 50 fewer to 13 fewer)	⊕⊕⊕◯ MODERATE Due to imprecision[77]	*RTS,S/AS01 vaccination probably reduces the risk of serious adverse events compared with control*
	RTS,S/AS01 versus control	Ph 2b randomised trial; 2017-2018 (month 0 to month 21, **20 months follow-up**)	38/298[78] (12.8%)	49 (16.7%)/293	RR .76 (0.52 to 1.13)	49/293 (167 per 1000)	40 fewer per 1,000 (from 80 fewer to 22 more)	⊕⊕◯◯ LOW Due to serious imprecision [79]	*There were too few events and small sample size to determine an association between RTS,S/AS01 vaccination and serious adverse events*
	RTS,S/AS01 alone versus SMC alone	Ph 3b randomised trial 2017 – 2020; **3 years follow-up**	3/1988 (0.2%)	0/1965 (0%)	Not estimable	-	-	⊕⊕◯◯ LOW Due to serious imprecision[80]	*Due to zero events in the control group, cannot determine an association between RTS,S/AS01 vaccination and serious adverse events*

[76] SAEs excluding malaria, included in intervention group participants receiving receive three doses of RTS,S/AS01 at months 0, 1,and 2 and a booster dose at month 20 (R3R group); or three doses of RTS,S/AS01 and a dose of comparator vaccine at month 20 (R3C group)

[77] Downgraded one level for imprecision: large confidence interval that incorporates no effect.

[78] SAEs excluding malaria

[79] Downgraded two levels for imprecision: large confidence interval that incorporates benefit and harm

[80] Downgraded wo levels for imprecision due to zero events in the control group

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
SERIOUS ADVERSE EVENTS (Safety, critical outcome)	**RTS,S/AS01 + SMC combination vs SMC alone**	Ph 3b randomised trial 2017 – 2020; **3 years follow-up**	2/1967 (0.1%)	0/1965 (0%)	Not estimable	-	-	⊕⊕◯◯ LOW Due to serious imprecision[81]	*Due to zero events in the control group, cannot determine an association between RTS,S/AS01 vaccination and serious adverse events*
	R21/Matrix-M versus control	Ph 2b randomised trial; 2019-2021;(12 months follow-up post dose 3)	4/140 (2.9%)	1/150 (0.7%)	RR 4.29 (0.48 to 37.88)	1/150 (7 per 1000)	22 more per 1000 (from 3 fewer to 246 more)	⊕⊕◯◯ LOW Due to serious imprecision[82]	*There were too few events and small sample size to determine an association between R21/Matrix-M vaccination and serious adverse events*
	R21/Matrix-M versus control	Ph 3 randomised trial; 2019-ongoing (**follow-up from dose 1 until 31 March 2023**)	88 (95 events); N= 3252 (2.7%)	41(47 events); N = 1626 (2.5%)	RR 1.07 (0.74 to 1.55)[83]	41/1626 (25 per 1000)	2 more per 1000 (from 7 fewer to 14 more)	⊕⊕⊕◯ MODERATE Due to imprecision[84]	*There is probably no difference in serious adverse events between R21/Matrix-M vaccination and control*

[81] Downgraded wo levels for imprecision due to zero events in the control group

[82] Downgraded two levels for imprecision: few events and CI that incorporates the possibility for benefit and harm.

[83] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)

[84] Downgraded one level for imprecision: few events and CI that incorporates the possibility for no/trivial effect and harm.

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
ALL-CAUSE MORTALITY (Safety, important outcome)	**Female:male impact of RTS,S/AS01 (3-dose and 4-dose) versus control**[85]	Post-hoc analysis of Ph 3 randomised trial 2009-2014 (**month 0 to study end; median 48 months follow-up**)			IRR 1.50 (1.03 to 2.08)[86]			⊕⊕◯◯ LOW Due to serious imprecision[87]	*RTS,S/AS01 vaccination may be associated with a higher mortality in girls compared with boys.*
	Female:male impact of RTS,S/AS01 alone versus SMC alone	Ph 3b randomised trial 2017 – 2020; **3 years follow-up**[15]			RR 1.80 (0.56 to 5.79)[88]			⊕⊕◯◯ LOW Due to serious imprecision[89]	*RTS,S/AS01 vaccination may result in little to no difference in all-cause mortality between girls and boys.*
	Female:male impact of RTS,S/AS01 and SMC combination versus SMC alone	Ph 3b randomised trial 2017 – 2020; **3 years follow-up**[18]			RR 0.35 (0.06 to 1.98)[90]			⊕⊕◯◯ LOW Due to serious imprecision[91]	*RTS,S/AS01 vaccination may result in little to no difference in all-cause mortality between girls and boys.*

[85] 8922 participants: 4-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20; 3-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a comparator vaccine at month 20; Control group received = comparator vaccine at months 0, 1, 2, and 20.

[86] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1): IRR of 4-dose group + 3-dose group vs Control group: Girls only IRR 2.0 (95% CI: 1.2 - 3.4) vs Boys only IRR 0.8 (95% CI 0.5 - 1.2). Girls only: 4-dose group 35 deaths (9 malaria)/1467 girls + 3-dose group 32 deaths (8 malaria) / 1500 girls vs Control group 17 deaths (4 malaria) / 1503 girls. Boys only 4-dose group 26 deaths (4 malaria) / 1509 boys + 3-dose group 19 deaths (9 malaria) / 1472 boys vs Control group 29 deaths (8 malaria) / 1471 boys

[87] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm.

[88] Girls only RTS,S vs SMC alone hazard ratio (HR) 1.23 (95% CI: 0.51 to 2.96); Boys only RTS,S vs SMC alone HR 0.68 (95% CI 0.32 to 1.47)

[89] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm.

[90] Girls only RTS,S+SMC combination group vs SMC alone group hazard ratio (HR) 0.22 (95% CI 0.05 to 1.02); Boys only RTS,S + SMC combination group vs SMC alone group HR 0.62 (95% CI 0.28 to 1.37)

[91] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm.

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
	Female:male ratio of RTS,S/AS01 implementing areas versus comparison areas	pilot implementation study* 2019-2021 (**month 0 to month 24**)[92]	-	-	Mortality ratio 1.08 (0.93 to 1.25)[93]	-		⊕⊕⊕◯ MODERATE Due to imprecision[94]	*There is probably no difference in all-cause mortality between girls and boys.*
	R21/Matrix-M versus control[22]	Ph 3 randomised trial; 2019-ongoing (**follow-up from dose 1 until 31 March 2023**)	15/3252 (0.5%)	4/1626 (0.2%)	RR 1.88 (0.62 to 5.64)[95]	4/1626	2 more per 1000 (1 fewer to 11 more)	⊕⊕◯◯ LOW Due to serious imprecision[96]	*There were too few deaths to determine an association with R21/Matrix-M vaccination.*
MENINGITIS (Safety, important outcome)	**RTS,S/AS01 versus control[1]**	Ph 3 randomised trial 2009-2014 (**month 0 to end of study; median 48 months' follow-up**)	R3R: 11/2976 + R3C: 1/2972	C3C: 1/2974	IRR: 10.5 (1.41 to 78.0)[97]	1/2974	3 more per 1000 (0 fewer to 26 more)	⊕⊕◯◯ LOW Due to serious imprecision[98]	*There were too few meningitis cases to determine an association with RTS,S/AS01 vaccination*

[92] Pilot implementation study designed to be analysed using cluster randomized control methodology. A total of 13682 deaths among children 1-59 months of age were reported via community-based mortality surveillance across the three countries from the start of vaccinations on 23 April 2019 to 31 March 2021 (deaths in April 2021 were excluded because verbal autopsies have not all been completed).

[93] There was no evidence that the effect of RTS,S/AS01 introduction on all-cause mortality differed between girls and boys in this age group. The mortality ratio in the vaccine-eligible age group (eligible for three doses) between implementing and comparison regions, was 0.93 (95%CI: 0.84 to 1.03), a 7% reduction (95%CI: -3% to 16%). There was no evidence that the mortality ratio differed between girls and boys, the p-value for this interaction was 0.343. The mortality ratio in girls was 0.98 and in boys 0.90.

[94] Downgraded one level because the evaluation was not powered at this time point to assess overall impact of vaccine introduction on mortality. However the evaluation was well powered to detect gender imbalance in all-cause mortality of the magnitude observed in the Phase 3 trial (mortality ratio = 1.4 - 1.6), in children up to about 2 years of age.

[95] SAEs leading to deaths (including SAEs leading to death which were considered accidental (injury) as per CIOMS/Narrative) in males and females in mITT population for both study populations (seasonal and age-based administration)

[96] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm

[97] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1); to be able to rule out an association with meningitis of the magnitude seen in the Phase 3 trial it would therefore be necessary to exclude rate ratios of about 10.5 (4.5 allowing for coverage and contamination) or more. There was no evidence that introduction of the malaria vaccine led to an increase in the incidence of hospital admission with meningitis.

[98] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm.

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
MENINGITIS (Safety, important outcome)	**RTS,S/AS01 alone versus SMC alone**[15]	Ph 3b randomised trial 2017 – 2020; **3 years follow-up**	0 cases	0 cases	Not estimable	-	-	⊕⊕◯◯ LOW Due to serious imprecision[99]	*RTS,S/AS01 vaccination may result in little to no difference in meningitis cases compared with SMC alone.*
	RTS,S/AS01 vaccination in implementing areas vs comparison areas[27]	pilot implementation study*, 2019-2021 (**month 0 to month 24**)	-	-	IRR: 0.81 (0.43 to 1.55)	-	-	⊕⊕⊕◯ MODERATE Due to imprecision[100]	*There is probably no difference in meningitis with RTS,S/AS01 vaccination.*
	RTS,S/AS01 versus control[7]	Ph 2b randomised trial 2017-2018 (20 months follow-up)	1 event; N = 298	2 events; N = 293	RR 0.49 (0.05 to 5.41)[101]	2/293	3 fewer per 1000 (6 fewer to 30 more)	⊕⊕◯◯ LOW Due to serious imprecision[102]	*There were too few meningitis cases and small sample size to determine an association with RTS,S/AS01 vaccination.*

[99] Downgraded two levels due to serious imprecision: no events reported in either group

[100] Downgraded one level due to imprecision: large confidence interval that incorporates the possibility of benefit and harm. It was only downgraded by 1 level because the result excludes an effect of the magnitude observed in the phase 3 trial, after allowing for uptake of the vaccine in the pilots.

[101] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1); exposed set receiving at least one vaccine dose.

[102] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm.

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
	R21/Matrix-M versus control[10]	Ph 3 randomised trial; 2019-ongoing (**follow-up from dose 1 until 31 March 2023**)	2/3252 (0.1%)	0/1626 (0%)	Not estimable	0/1626	-	⊕⊕◯◯ LOW Due to serious imprecision[103]	*R21/Matrix- M vaccination may result in little to no difference in meningitis cases compared to control.*
FEBRILE CONVULSIONS (within 28 days of vaccination) (Safety, important outcome)	RTS,S/AS01 versus control[1]	Ph 3 randomised trial 2009-2014 (**month 0 to end of study; median 48 months' follow-up**)	159/2976 (5.3%)	164/2974 (5.5%)	RR: 0.97 (0.78 to 1.20)	164/2974	2 fewer per 1000 (12 fewer to 11 more)	⊕⊕◯◯ LOW Due to serious imprecision[104]	*RTS,S malaria vaccination may result in little or no difference in febrile convulsions*
	RTS,S/AS01 alone versus SMC alone[15]	Ph 3b randomised trial 2017 – 2020; **3 years follow-up**	3/1988 (0.2%)	0/1965 (0.0%)	Not estimable	-		⊕⊕◯◯ LOW Due to serious imprecision[105]	*RTS,S malaria vaccination may result in little or no difference in febrile convulsions compared with SMC alone*
	RTS,S/AS01 + SMC combination vs SMC alone[18]	Ph 3b randomised trial 2017 – 2020; **3 years follow-up**	2/1967 (0.3%)	0/1965 (0.0%)	Not estimable	-		⊕⊕◯◯ LOW Due to serious imprecision[106]	*The combination of RTS,S malaria vaccination with SMC may result in little or no difference in febrile convulsions compared with SMC alone.*

[103] Downgraded two levels due to serious imprecision: very few events and 0 events in the control arm.
[104] Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm.
[105] Downgraded two levels due to serious imprecision: very few events and 0 events in the control arm.
[106] Downgraded two levels due to serious imprecision: very few events and 0 events in the control arm.

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
FEBRILE CONVULSIONS (within 28 days of vaccination) (Safety, important outcome)	**R21/Matrix-M versus control**[20]	Ph 2b randomised trial; 2019-2021; (**12 months follow-up post dose 3)**	0/138	0/140	Not estimable	-		⊕⊕◯◯ LOW Due to serious imprecision[107]	*Due to zero events and small sample size, we cannot determine the association of R21/Matrix-M vaccination with febrile convulsions*
	R21/Matrix-M versus control[22]	Ph 3 randomised trial; 2019-ongoing (**follow-up from dose 1 until 31 March 2023**)	8 events/3252 (12,602 doses)	1 event/1626	RR 4.00 (0.50 to 31.95)[108]	2 more per 1,000 (from 0 fewer to 19 more)		⊕⊕⊕◯ MODERATE Due to imprecision[109]	*R21/Matrix-M probably results in an increased risk of febrile convulsions.* *In the vaccinated group, 5 events occurred in days 0-3 after vaccination, and 3 events occurred in days occurred in days 4-28*[110]

[107] Downgraded two levels due to serious imprecision: no events in either group and small sample size.

[108] Modified ITT analysis

[109] Downgraded one level for imprecision: few events and CI that includes no effect and harm

[110] A post-hoc analysis of clustering of febrile convulsions within 0-3 days of vaccination vs 4-28 days of vaccination shows the risk difference for the R21/Matrix-M arm is 0.00036 (0.000008 to 0.00071), p=0.004, 95% CI 2.0 to 67.1; risk difference for the control is 0.00016 (-0.00015 to 0.00047), p = 0.28; RI. The risk difference of 0.00036 translates to an attributable risk in the R21/Matrix-M arm of 1/2800 doses administered. This shows evidence of clustering of febrile convulsions in R21/Matrix-M (p=0.004) but not in the control (p=0.28).

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
CEREBRAL MALARIA (Safety, important outcome)	**RTS,S/AS01 (3-dose + 4 dose combination) versus control**[111]	Post-hoc analysis of Ph 3 randomised trial 2009-2014 (**month 0 to trial end; median 48 months' follow-up**)	19/2976 (3-dose) + 24/2974 (4-dose)	10/2974	IRR: 2.15 (1.1 to 4.3)[112]	10/2974	4 more per 1000 (4 more to 11 more)	⊕◯◯◯ VERY LOW Due to serious risk of bias and imprecision[113]	*It is very uncertain whether malaria vaccination is associated with an increase in cerebral malaria cases.*
	RTS,S/AS01 vaccination in implementing areas vs comparison areas[27]	pilot implementation study* 2019-2021 (**month 0 to month 24**)	-	-	IRR: 0.77 (0.44 to 1.35)[114]	-	-	⊕⊕⊕◯ MODERATE Due to imprecision[115]	*There is probably no difference in cerebral malaria RTS,S/AS01 vaccination.*
	RTS,S/AS01 versus control[7]	Ph 2b randomised trial 2017-2018 (**20 months follow-up**)	0 events; N = 298	1 event; N = 293	RR 0.33 (0.01 to 8.04)[116]	1/293	2 fewer per 1000 (3 fewer to 24 more)	⊕⊕◯◯ LOW Due to serious imprecision[117]	*RTS,S/AS01 vaccination may result in little or no difference in cerebral malaria.*

[111] 8922 participants: Unplanned sub-group analysis of participant groups: 4-dose group received three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20; 3-dose group received three doses of RTS,S/AS01 and a dose of comparator vaccine at month 20; Control group received a comparator vaccine at months 0, 1, 2, and 20 (control group). For this safety outcome we have reported the combined results for children receiving 3 or 4 doses of the vaccine; however, it has not been downgraded for indirectness.

[112] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)

[113] Downgraded two levels for risk of bias: unclear risk of bias due to heavy involvement of the funder within the project. In addition, this was a post-hoc analysis based on an imprecise algorithm, followed by record review and expert panel review. Cerebral malaria is a difficult diagnosis to make in real time, and worse through record review. Downgraded one level due to imprecision: wide confidence interval that incorporates the possibility of benefit and of no effect.

[114] To be able to rule out an association with cerebral malaria of the magnitude seen in the Phase 3 trial it would therefore be necessary to exclude rate ratios of about 2.2 (1.6 allowing for 60% coverage and 5% contamination) or more. There was no evidence that introduction of the malaria vaccine led to an increase in the incidence of hospital admission with cerebral malaria. The IRR excludes an effect of the magnitude observed in the Phase 3 trial (RR = 2.2), after allowing for uptake of the vaccine in the pilot

[115] Downgraded one level due to imprecision: large confidence interval that incorporates the possibility of benefit and harm. It was only downgraded by 1 level because the result excludes an effect of the magnitude observed in the phase 3 trial, after allowing for uptake of the vaccine in the pilots.

[116] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1); exposed set receiving at least one vaccine dose.

[117] Downgraded two levels due to serious imprecision: very few events and 0 events in the intervention arm.

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
	RTS,S/AS01 + SMC combination vs SMC alone[15]	Ph 3b randomised trial 2017 – 2020; **3 years follow-up**	4 events (vaccine alone) + 1 case (vaccine + SMC)	0 events	Not estimable[118]	-	-	⊕⊕◯◯ LOW Due to serious imprecision[119]	*The combination of RTS,S malaria vaccination with SMC may result in little or no difference in cerebral malaria compared with SMC alone.*
	R21/Matrix-M versus control[10]	Ph 3 randomised trial; 2019-ongoing (**follow-up from dose 1 until 31 March 2023**)	1/3249	1/1626	RR 0.50 (0.03 to 8.00)[120]	1/1626	0 fewer per 1000 (from 1 fewer to 4 more)	⊕⊕◯◯ LOW Due to serious imprecision[121]	. *Too few events to determine an association between R21/Matrix-M vaccination and cerebral malaria,*

[118] Due to the absence of cases in the reference group, it was not possible to calculate the incidence rate ratio in vaccine recipients. There were no cases of cerebral malaria in the SMC alone group, 4 cases in the RTS,S vaccine alone group (0.723 cases per 1000 PYAR; 95%CI 0.271 to 1.93), and 1 case in the combination of RTS,S vaccine + SMC group (0.182 cases per 1000 PYAR; 95%CI 0.026 to 1.29).
[119] Downgraded two levels due to serious imprecision: very few events and 0 events in the control arm.
[120] **Modified ITT analysis** (participants receiving at least one vaccine dose, with follow-up beginning from dose 1)
[121] Downgraded two levels due to serious imprecision: very few events and large confidence interval .

Outcome	Comparison	Study design	№ of participants		Relative effect (95% CI)	Absolute effects (95% CI)		Certainty	Comments
			Vaccination	Control		Control	Risk difference with malaria vaccination		
	Included Studies – RTS,S/AS01 1. Greenwood BM on behalf of the RTS,S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. Lancet. 2015;386(9988):31-45. (MAIN STUDY) 1. b) Mendoza YG, Garrica E, Leacha A, Lievensa M, Ofori-Anyinama O, Pirçona JY, et al. Safety profile of the RTS,S/AS01 malaria vaccine in infants and children: additional data from a phase III randomized controlled trial in sub-Saharan Africa. Human Vaccines & Immunotherapeutics. 2019;15(10):2386–2398. (COMPANION STUDY) 1. c) Tinto H, Otieno W, Gesase S, Sorgho H, Otieno L, Liheluka E, et al. John Long-term incidence of severe malaria following RTS,S/AS01 vaccination in children and infants in Africa: an open-label 3-year extension study of a phase 3 randomised controlled trial. Lancet Infect Dis. 2019;19(8):821-832. (COMPANION STUDY) 2. Chandramohan D, Zongo I, Sagara I, Cairns M, Yerbanga RS, Diarra M et al. Seasonal malaria vaccination with or without seasonal malaria chemoprevention. N Engl J Med. 2021;385:1005-1017. (MAIN STUDY) 2. a) Cairns M, Barry A, Zongo I, Sagara I, Yerbanga SR, Diarra M, et al. The duration of protection against clinical malaria provided by the combination of seasonal RTS,S/AS01E vaccination and seasonal malaria chemoprevention versus either intervention given alone. BMC Medicine 2022;20(1): 352. (COMPANION STUDY) 3. Milligan P, Moore K: Statistical report on the results of the RTS,S/AS01 Malaria Vaccine Pilot Evaluation 24 months after the vaccine was introduced. 2021;V1.3 6 Sept 2021 (MAIN STUDY) 4. Samuels AM, Ansong D, Kariuki SK, Adjei S, Bollaerts A, Ockenhouse C, et al. Efficacy of RTS,S/AS01E malaria vaccine administered according to different full, fractional, and delayed third or early fourth dose regimens in children aged 5-17 months in Ghana and Kenya: an open-label, phase 2b, randomised controlled trial. Lancet Infect. Dis. 2022;22(9): 1329-1342. (MAIN STUDY) **Included Studies – R21/Matrix-M** 5. Datoo MS, Natama MH, Some A, Traore O, Rouamba T, Bellamy D, et al. Efficacy of a low-dose candidate malaria vaccine, R21 in adjuvant Matrix-M, with seasonal administration to children in Burkina Faso: a randomised controlled trial. Lancet. 2021;397(10287): 1809. (MAIN STUDY) 6. NCT04704830. R21/Matrix-M in African Children Against Clinical Malaria. Data provided by WHO. (MAIN STUDY)								

Cause of death

Study: **R21/Matrix-M versus control** (NCT04704830)

Listing of SAEs leading to death by vaccination strategy, study arm, and cause of death

SAEs leading to death are ordered by vaccination strategy (seasonal and standard), study arm (R21/Matrix-M and control (rabies) vaccine), cause of death - severe malaria (highlighted in grey) vs. other causes, and time since last dose at SAE onset (days in ascending order).

Vaccination strategy	Study arm	Cause of death (as reported in the study)	Gender	Age (in months)	Last dose given prior to SAE	Time since last dose at SAE onset (days)	Death associated with vaccine?
Seasonal	R21/Matrix-M	Severe malaria	Female	13	Dose 4	73	No relationship
Seasonal	R21/Matrix-M	Severe malaria or septicaemia	Female	9	Dose 4	85	No relationship
Seasonal	R21/Matrix-M	Severe malaria	Male	5	Dose 4	223	No relationship
Seasonal	R21/Matrix-M	Severe malaria	Male	9	Dose 3	346	No relationship
Seasonal	R21/Matrix-M	Bronchitis	Female	5	Dose 3	8	No relationship
Seasonal	R21/Matrix-M	Severe anaemia*	Male	6	Dose 4	126	No relationship
Seasonal	R21/Matrix-M	Respiratory infection	Male	28	Dose 4	126	No relationship
Seasonal	R21/Matrix-M	Superficial dermal burn of the neck and face	Female	6	Dose 3	258	No relationship
Seasonal	Rabies vaccine	Severe malaria	Male	5	Dose 4	36	No relationship
Seasonal	Rabies vaccine	Death due to unknown cause	Female	14	Dose 4	119	No relationship
Standard	R21/Matrix-M	Severe malarial anaemia	Male	12	Dose 1	13	No relationship
Standard	R21/Matrix-M	Suspected aspiration	Male	5	Dose 4	84	No relationship
Standard	R21/Matrix-M	Scalding	Male	28	Dose 4	103	No relationship
Standard	R21/Matrix-M	Fall into a well	Male	6	Dose 3	156	No relationship
Standard	R21/Matrix-M	Bacterial meningitis	Male	9	Dose 3	177	No relationship
Standard	R21/Matrix-M	Acute gastroenteritis with severe dehydration and subsequent hypovolemic shock	Female	6	Dose 3	190	No relationship
Standard	R21/Matrix-M	Unknown cause	Male	9	Dose 3	244	No relationship
Standard	Rabies vaccine	Severe malaria	Female	17	Dose 3	250	No relationship
Standard	Rabies Vaccine	Drowning	Female	10	Dose 3	102	No relationship

*severe anaemia without parasitaemia