Annex 9: GRADE and Evidence to Recommendation tables on RTS,S/AS01 malaria vaccine

Content:

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Annex 9a: Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Evidence summary table

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Question: Should a minimum of 4 doses of RTS,S/AS01 be provided to reduce malaria disease burden in children >= 5 months of age living in countries in sub-Saharan Africa with moderate to high malaria transmission?

Population: Children ≥ 5 months of age living in countries in sub-Saharan Africa with moderate to high malaria transmission

Intervention: A minimum of 4 doses of RTS,S/AS01 (given as a 3-dose initial series; first dose should be provided between 5 and 17 months of age) with a minimal interval between doses of 4 weeks

Comparison: Malaria interventions currently in place without malaria vaccination

Setting: countries in sub-Saharan Africa with moderate to high malaria transmission

Outcome	№ of studies	Certainty assessment						№ of patients		Effect		Certainty	Comments
		Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTS,S/AS01	No vaccination	Relative (95% CI)	Absolute (95% CI)		
CLINICAL MALARIA (Efficacy, important outcome)	**Clinical malaria episodes (from month 0 to end of study; median follow-up: 48 months) (modified ITT analysis)** (assessed with: Illness in a child brought to a study facility with a measured temperature of 37·5°C and P. falciparum asexual = parasitaemia at a density of > 5000 parasites per cubic millimetre or a case of malaria meeting the primary case definition of severe malaria. Severe malaria primary case definition = P. falciparum asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one)												
	1 [1] (RTS,S/AS01)	randomised trials	not serious [a]	not serious	not serious	not serious	none	R3R: N=2976; 6616 episodes	C3C: N=2974; 9585 episodes	VE: 36.3% (31.8 to 40.5)	-	⊕⊕⊕⊕ HIGH	PP analysis VE: 39% (95% CI 34.3 to 43.3)
	Clinical malaria events (at 3 years) (assessed with: measured temperature ≥ 37.5 °C, or a history of fever within the past 48 hours, and P. falciparum parasitemia ≥ 5,000/mm3 in children presenting at a study health facility)												
	1 [2] (Chandramohan)	***RTS,S/AS01 vs SMC alone***											
		randomised trials	not serious	not serious	not serious	not serious	none	Incidence: 278 (264.6 to 292.4)/1000 PYAR; 1540 events over 5535.7 PYAR	Incidence: 305 (290.5 to 319.8)/1000 PYAR; 1661 events over 5449.9 PYAR	HR 0.92 (99% CI 0.82 to 1.04)	-	⊕⊕⊕⊕ HIGH	"The 90, 95, and 99% CI for the HR all excluded the pre-specified non-inferiority margin of 1.20."
		SMC + RTS,S/AS01 vs SMC alone											
		randomised trials	not serious	not serious	not serious	not serious	none	Incidence: 113 (104.7 to 122.5)/1000 PYA); 624 events over 5508 PYAR	Incidence: 305 (290.5 to 319.8)/1000 PYAR; 1661 events over 5449.9 PYAR	PE: 62.8% (58.4 to 66.8)	-	⊕⊕⊕⊕ HIGH	

SEVERE MALARIA (Efficacy, critical outcome)	**Severe malaria episodes (from month 0 to end of study) (modified ITT analysis)** **(assessed with: P. falciparum asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity and without diagnosis of a coexisting illness. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of 2 (on a scale of 0 to = 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration)**												
	1 [1] (RTS,S/AS01)	randomised trials	not serious [a]	not serious	not serious	not serious	none	R3R: N=2976; 116 episodes	C3C: N=2974; 171 episodes	VE: 32.2% (13.7 to 46.9)	-	⊕⊕⊕⊕ HIGH	PP analysis VE 28.5% (6.3 to 45.7)
	Hospitalization due to severe malaria												
	1 [2] (Chandramohan)	***RTS,S/AS01 vs SMC alone***											
		randomised trials	not serious	not serious	not serious	very serious [b]	none	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% (-65.8 to 25.7)		⊕⊕◯◯ LOW	Most cases of severe malaria were severe malaria anaemia (vaccine: 25/37; SMC: 31/37)
		SMC + RTS,S/AS01 vs SMC alone											
		randomised trials	not serious	not serious	not serious	serious [c]	none	11 events; 2.0 (1.1 to 3.6) per 100 PYAR	37 events; 6.8 (4.9 to 9.4) per 1000 PYAR	PE: 70.5% (41.9 to 85.0)		⊕⊕⊕◯ MODERATE	Most cases of severe malaria were severe malaria anaemia (vaccine + SMC: 10/11; SMC: 31/37)
	Severe malaria (from month 0 to 24 months)												
	1 [3] (MVPE)	pilot implementation study*	not serious [d]	not serious	not serious	serious [e]	none	-	-	IRR 0.70 (0.54 to 0.92)	-	⊕⊕⊕◯ MODERATE	
SEVERE ANEMIA (Impact, important outcome).	**≥1 episode of incident severe malaria anaemia (from month 0 to end of study) (modified ITT analysis)** **(assessed with: a documented haemoglobin < 5·0 g per decilitre identified at clinical presentation to morbidity surveillance system in association with a P. falciparum parasitaemia at a density of > 5000 parasites per cubic millimetre)**												
	1 [1] (RTS,S/AS01)	randomised trials	not serious [a]	not serious	not serious	serious [c]	none	R3R: 23/2976 (0.8%)	C3C: 44/2974 (1.5%)	VE 47.8% (11.6 to 69.9)	-	⊕⊕⊕◯ MODERATE	
	WHO-defined severe malaria anaemia												
	1 [2]	***RTS,S/AS01 vs SMC alone***											

	(Chandramohan)	randomised trials	not serious	not serious	not serious	very serious [b]	none	25 events; 4.52 (3.05 to 6.68) per 1000 PYAR	31 events; 5.69 (4.00 to 8.09) per 1000 PYAR	PE: 18.4% (-39.3 to 52.2)	-	⊕⊕◯◯ LOW	
		SMC + RTS,S/AS01 vs SMC alone											
		randomised trials	not serious	not serious	not serious	serious [c]	none	10 events; 1.82 (0.977 to 3.37) per 1000 PYAR	31 events; 5.69 (4.00 to 8.09) per 1000 PYAR	PE: 67.9% (34.1 to 84.3)	-	⊕⊕⊕◯ MODERATE	
BLOOD TRANSFUSION (Impact, critical outcome)	**Blood transfusion (from month 0 to end of study) (modified ITT analysis)**												
	1 [1] (RTS,S/AS01)	randomised trials	not serious [a]	not serious	not serious	serious [c]	none	R3R: 78/2976 (2.6%)	C3C: 109/2974 (3.7%)	VE 28.5% (3.5 to 47.2)	-	⊕⊕⊕◯ MODERATE	
	Blood transfusion (at 3 years)												
	1 [2] (Chandramohan)	***RTS,S/AS01 vs SMC alone***											
		randomised trials	not serious	not serious	not serious	very serious [b]	none	21 events; 3.79 (2.47 to 5.82) per 1000 PYAR	23 events; 4.22 (2.80 to 6.35) per 1000 PYAR	PE: 8.27% (-67.6 to 49.8)	-	⊕⊕◯◯ LOW	
		SMC + RTS,S/AS01 vs SMC alone											
		randomised trials	not serious	not serious	not serious	serious [c]	none	8 events; 1.45 (0.726 to 2.90) per 1000 PYAR	23 events; 4.22 (2.80 to 6.35) per 1000 PYAR	PE: 65.4% (22.9 to 84.5)	-	⊕⊕⊕◯ MODERATE	
CEREBRAL MALARIA (safety, critical outcome)	**Possible cerebral malaria**												
	1 [1] (RTS,S/AS01)	randomised trials	very serious [f]	not serious	not serious [g]	serious [c]	none	R3R: 19/2976 + R3C: 24 /2974	C3C: 10/2974	IRR: 2.15 (95% CI 1.1 to 4.3)	-	⊕◯◯◯ VERY LOW	
	WHO defined cerebral malaria												
	1 [2] (Chandramohan)	***RTS,S/AS01 vs SMC alone***											
		randomised trials	not serious	not serious	not serious	serious [h]	none	4 events; 0.723 (0.271 to 1.93) per 1000 PYAR	0 events	-	-	⊕⊕◯◯ LOW	
		SMC + RTS,S/AS01 vs SMC alone											

		randomised trials	not serious	not serious	not serious	serious [h]	none	1 event; 0.182 (0.026 to 1.29) per 1000 PYAR	0 events			⊕⊕◯◯ LOW	
	Hospital admission with cerebral malaria (month 0 to month 24) **(positive for P.falciparum by rapid diagnostic test or microscopy, with impaired consciousness (i.e. a Glasgow coma score <11 or Blantyre coma score <3 or assessed as P or U on the AVPU ("Alert, Voice, Pain, Unresponsive") score, excluding cases with probable meningitis)**												
	1 [3] **(MVPE)**	pilot implementation study*	not serious [d]	not serious	not serious	serious [i]	none	-	-	IRR: 0.77 (95% CI 0.44 to 1.35)	-	⊕⊕⊕◯ MODERATE	The 95% confidence intervals for pooled estimates obtained during this evaluation exclude an effect of the magnitude observed in Phase III trial, after allowing for the levels of uptake of the vaccine[†]
HOSPITAL ADMISSION **(impact, critical outcome)**	**All-cause hospital admission (month 0 to study end) (modified ITT analysis)**												
	1 [1] **(RTS,S/AS01)**	randomised trials	not serious [a]	not serious	not serious	not serious	none	R3R: 644/2976 (21.6%)	C3C: 771/2974 (25.9%)	VE 16.5% (7.2 to 24.9)	-	⊕⊕⊕⊕ HIGH	
	All-cause hospital admission (excluding external causes and surgery)												
	1 [2] **(Chandramohan)**	***RTS,S/AS01 vs SMC alone***											
		randomised trials	not serious	not serious	not serious	very serious [b]	none	73 events; 13.2 (10.5 to 16.6) per 1000 PYAR	60 events; 11.0 (8.55 to 14.2) per 1000 PYAR	PE: -22.3% (-74.4 to 14.3)	-	⊕⊕◯◯ LOW	
		SMC + RTS,S/AS01 vs SMC alone											
		randomised trials	not serious	not serious	not serious	very serious [b]	none	49 events; 8.90 (6.72 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)	-	⊕⊕◯◯ LOW	
	All-cause hospital admission (month 0 to month 24) **A stay in hospital/inpatient facility for at least one night, (and patients who were admitted but died before an overnight stay was completed)**												

	1 [3] **(MVPE)**	pilot implementation study*	not serious [d]	not serious	not serious	serious [j]	none	-	-	PE 8.0% (-3.0 to 17.0)	-	⊕⊕⊕◯ MODERATE	
	Hospital admission (with a positive malaria test) (month 0 to month 24)												
	1 [3] **(MVPE)**	pilot implementation study*	not serious [d]	not serious	not serious	not serious	none	-	-	PE: 21% (7.0 to 32)	-	⊕⊕⊕⊕ HIGH	
ALL-CAUSE MORTALITY (impact and safety, critical outcome)	**All-cause mortality (month 0 to study end) (modified ITT analysis)**												
	1 [1] **(RTS,S/AS01)**	***All population***											
		randomised trials	not serious [a]	not serious	not serious [g]	very serious [b]	none	R3R: 61 (13 malaria)/2976 + R3C: 51 (17 malaria)/2972	C3C: 46 (13 malaria)/2974	-	-	⊕⊕◯◯ LOW	
		Girls only (safety assessment)											
		randomised trials	see above	see above	see above	see above	see above	R3R: 35 (9 malaria)/1467 + R3C: 32 (8 malaria)/1500	C3C: 17 (4 malaria)/1503	IRR: 2.0 (95% CI 1.2 to 3.4)	-	see above	Female/male risk ratio (95% CI) 1.50 (1.03 to 2.18)
		Boys only (safety assessment)											
		randomised trials	see above	see above	see above	see above	see above	R3R: 26 (4 malaria)/1509 + R3C: 19 (9 malaria)/1472	C3C: 29 (8 malaria)/1471	IRR: 0.8 (95% CI 0.5 to 1.2)	-	see above	
	All-cause mortality (excluding external causes and surgery)												
	1 [2] **(Chandramohan)**	***RTS,S/AS01 vs SMC alone***											
		All population											
		randomised trials	not serious	not serious	not serious	very serious [b]	none	22 events; 3.97 (2.62 to 6.04) per 1000 PYAR	25 events; 4.59 (3.10 to 6.79) per 1000 PYAR	PE: 12.1% (-55.7 to 50.4)	-	⊕⊕◯◯ LOW	
		Girls only (safety assessment)											

	randomised trials	see above	see above	see above	see above	see above	11 events; 4.15 (2.30, 7.49) per 1000 PYAR	9 events; 3.42 (1.78, 6.57) per 1000 PYAR	HR (95% CI) 1.23 (0.51 to 2.96)		see above	Gender Interaction parameter [$] (95% CI) 1.80 (0.56 to 5.79)
	Boys only (safety assessment)											
	randomised trials	see above	see above	see above	see above	see above	11 events; 3.82 (2.11, 6.89) per 1000 PYAR	16 events; 5.68 (3.48, 9.27) per 1000 PYAR	HR (95% CI) 0.68 (0.32 to 1.47)		see above	
	SMC + RTS,S/AS01 vs SMC alone											
	All population											
	randomised trials	not serious	not serious	not serious	serious [c]	none	12 events; 2.18 (1.24 to 3.84) per 1000 PYAR	25 events; 4.59 (3.10 to 6.79) per 1000 PYAR	PE: 52.3% (4.99 to 76.0)	-	⊕⊕⊕◯ MODERATE	
	Girls only (safety assessment)											
	randomised trials	see above	see above	see above	see above	see above	2 events; 0.75 (0.19, 3.01) per 1000 PYAR	9 events; 3.42 (1.78, 6.57) per 1000 PYAR	HR (95% CI) 0.22 (0.05 to 1.02)		see above	Gender Interaction parameter [$] (95% CI) 0.35 (0.06, 1.98)
	Boys only (safety assessment)											
	randomised trials	see above	see above	see above	see above	see above	10 events; 3.51 (1.89, 6.52) per 1000 PYAR	16 events; 5.68 (3.48, 9.27) per 1000 PYAR	HR (95% CI) 0.62 (0.28 to 1.37)		see above	
All-cause mortality (excluding deaths due to injury) (month 0 to month 24)												
1 [3] (MVPE)	***All population***											
	pilot implementation study*	not serious [d]	not serious	not serious	serious [k]	none	-	-	Mortality ratio 0.93 (0.84 to 1.03)	-	⊕⊕⊕◯ MODERATE	
	Girls only (safety assessment)											

		pilot implementation study*	see above	see above	see above	see above	see above	-	-	Mortality ratio 0.98 (0.87 to 1.09)	-	see above	Gender interaction: (female:male ratio of mortality ratios): 1.08 (0.93, 1.25); p = 0.321 Excludes interaction of the magnitude observed in the Phase 3 trial after allowing for uptake of the vaccine in the pilots (1.4)
		Boys only (safety assessment)											
		pilot implementation study*	see above	see above	see above	see above	see above	-	-	Mortality ratio 0.91 (0.80 to 1.04)	-	see above	
MENINGITIS (safety, critical outcome)	**Meningitis (month 0 to study end) (mITT analysis)**												
	1 [1] (RTS,S/AS01)	randomised trials	serious [l]	not serious	not serious [g]	serious [c]	none	R3R: 11/2976 + R3C: 1/2972	C3C: 1/2974	IRR: 10.5 (95% CI 1.41 to 78.0)	-	⊕⊕◯◯ LOW	
	Meningitis (confirmed by lumbar puncture)												
	1 [2] (Chandramohan)	***RTS,S/AS01 vs SMC alone***											
		randomised trials	not serious	not serious	not serious	very serious [m]	none	0 cases	0 cases	-	-	⊕⊕◯◯ LOW	
		SMC + RTS,S/AS01 vs SMC alone											
		randomised trials	not serious	not serious	not serious	very serious [m]	none	0 cases	0 cases	-	-	⊕⊕◯◯ LOW	
	Hospital admission with meningitis												

	1 [3] **(MVPE)**	pilot implementation study*	not serious [d]	not serious	not serious	serious [n]	none	-	-	IRR: 0.81 (95% CI 0.43 to 1.55)	-	⊕⊕⊕◯ MODERATE	Excludes effect of the magnitude observed in the phase 3 trial, after allowing for uptake of the vaccine in the pilots.††

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Abbreviations

CI: Confidence interval; IRR; incidence rate ratio; ITT: intention-to-treat; PE: protective efficacy; PYAR: person years at risk; VE: vaccine efficacy

R3R: 3× RTS,S plus booster RTS,S; R3C: 3× RTS,S plus comparator vaccine; C3C: controls (comparator vaccines)

Explanations

* Pilot implementation study designed to be analyzed as cluster randomised controlled trial

† To be able to rule out an association with cerebral malaria of the magnitude seen in the phase 3 trial we would therefore want to be able to exclude rate ratios of about 2.2 (1.6 allowing for 60% coverage and 5% contamination) or more

†† To be able to rule out an association with meningitis of the magnitude seen in the phase 3 trial we would therefore want to be able to exclude rate ratios of about 10.5 (4.5 allowing for coverage and contamination) or more.

$ Interaction parameter and 95% CI indicates evidence for effect modification by gender (1 indicates no effect modification)

a. Study was rated as unclear risk of bias due to heavy involvement of the funder within the project; however, it has not been downgraded for ROB as this was the only concern and the study is otherwise well conducted.

b. Downgraded two levels due to imprecision: few events and a very large confidence interval that incorporates the possibility of benefit and harm

c. Downgraded one level due to imprecision: few events and large confidence interval

d. Not downgraded for risk of bias despite being an open-label study because the findings from the household survey suggest there is no evidence that the introduction of RTS,S/AS01 had a negative effect on uptake of other childhood vaccines, ITN use, care-seeking behavior, or health worker behavior in testing and treating for febrile illness.

e. Downgraded one level for imprecision: large confidence interval that incorporates the possibility of benefit and little to no effect.

f. 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.

g. 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.

h. Downgraded two levels due to imprecision: very few events and 0 events in the control arm

i. Downgraded one level due to imprecision: large confidence interval that incorporates the possibility of benefit and harm. Study was powered for a pooled analysis only, country estimates vary but confidence intervals are wide and consistent with pooled effect.

j. Downgraded one level due to imprecision as the large confidence interval incorporates de posibiliity of benefit and harm. Not downgraded a second level despite being powered for a pooled analysis only, country estimates vary but confidence intervals are wide and consistent with pooled effect.

k. Downgraded one level for imprecision: analysis not powered at this time point to assess impact of vaccine introduction on mortality, but the pooled point estimate for mortality is consistent with the expected impact (3% - 8% depending on the proportion of deaths attributable to malaria.

l. Downgraded one level for risk of bias: unclear risk of bias due to heavy involvement of the funder within the project. In addition, this outcome was not pre-specified in the protocol (post-hoc analysis).

m. Downgraded two levels for imprecision: no events reported in either group.

n. 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.

References

1. RTS, S Clinical 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. The Lancet; 2015.

2. Chandramohan D, Zongo I,Sagara I,Cairns M,Yerbanga RS,et al. Seasonal malaria vaccination with or without seasonal malaria chemoprevention. New England Journal of Medicine; 2021.

3. P Milligan and K Moore, Statistical report on the results of the RTS,S/AS01 Malaria Vaccine Pilot Evaluation 24 months after the vaccine was introduced. V1.3 Aug 2021.

Annex 9b: Malaria Policy Advisory Group (MPAG) and Strategic Advisory Group of Experts (SAGE) on Immunization - Evidence to recommendations framework

Question: Should a minimum of 4 doses of RTS,S/AS01 be provided to reduce malaria disease burden in children >= 5 months of age living in countries in sub-Saharan Africa with moderate to high malaria transmission?

Population: Children >= 5 months of age living in countries in sub-Saharan Africa with moderate to high malaria transmission

Intervention: A minimum of 4 doses of RTS,S/AS01 (given as a 3-dose initial series; dose 1 should be provided between 5 and 17 months of age) with a minimal interval between doses of 4 weeks

Comparison(s): Malaria interventions currently in place without malaria vaccination

Outcome: Clinical malaria, severe malaria, anaemia, blood transfusion, cerebral malaria, hospital admission, all-cause mortality, safety (AE, SAE, AEFI, AESI), tolerability

Background:

WHO estimated in the 2020 World Malaria Report that, in 2019, approximately 229 million cases and 409 000 deaths were attributable to malaria, with 94% of these deaths occurring in sub-Saharan Africa. Most malaria deaths in Africa occur in children younger than 5 years. Infants and young children in malaria-endemic countries in Africa typically experience several clinical episodes of malaria before they acquire partial immunity, which in older childhood protects against severe and fatal malaria.

Between 2000 and 2015, global malaria case incidence declined by 27%. Globally, an estimated 1.5 billion malaria cases and 7.6 million malaria deaths have been averted in the period 2000–2019.

However, between 2015 and 2019 the annual case incidence decreased by less than 2%, indicating a slowing of the rate of decline since 2015.[4] This levelling off of incidence (in some countries an increase occurred) has been attributed mainly to the stalling of progress in several countries with moderate or high transmission. [iii] There is general agreement that to get malaria control back on track, new tools are needed alongside efforts to increase uptake and use of current malaria control tools.

The Malaria Vaccine Implementation Programme (MVIP) was developed in response to the 2015 joint recommendation by SAGE and MPAC to introduce the RTS,S/AS01 (RTS,S) malaria vaccine in phased introductions in 3-5 African countries. Recognizing the potential of the vaccine to reduce clinical and severe malaria in African children, the pilots were designed to answer outstanding questions on safety, impact in routine use, and feasibility of reaching children with the recommended 4-dose schedule. The ministries of health (MoH) of the three pilot countries, Ghana, Kenya and Malawi, are delivering the RTS,S vaccine in selected areas through their child immunization services. Data are collected through the Malaria Vaccine Pilot Evaluation (MVPE) to inform WHO recommendations on the broader use of RTS,S in sub-Saharan Africa.

In 2019, the SAGE and MPAC endorsed the Framework for WHO recommendation on RTS,S/AS01[1] which outlines a step-wise approach for review and WHO recommendation on broader use of RTS,S based on emerging pilot data. In the Framework it was agreed that a WHO policy recommendation on the use of RTS,S/AS01 beyond the pilot countries could be made if and when (i) concerns regarding the safety signals observed in the Phase 3 trial are satisfactorily resolved, and (ii) severe malaria or mortality data trends are assessed as consistent with a beneficial impact of the vaccine. The 2019 Framework further states that a recommendation could be made in absence of data showing vaccine impact on mortality (impact on severe malaria is an acceptable surrogate); a recommendation need not be predicated on attaining high coverage, including coverage of dose 4; and cost effectiveness estimates should be regularly refined as data become available for increasingly precise calculation, and presented at appropriate time points.

The rate of events in the malaria vaccine pilot evaluations allowed for sufficient data availability to conduct the primary analysis per the statistical analysis plan (SAP) on safety and impact on hospitalized severe malaria 24 months after the start of RTS,S vaccination in the first pilot country(end of April 2021).

[1] Framework for Recommendation on RTS,S, April 2019: https://www.who.int/malaria/mpac/proposed-framework-for-policy-decision-on-rtss-as01-malaria-vaccine.pdf

Evidence-to-recommendations framework: RTS,S/AS01 malaria vaccine

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	Despite considerable efforts and the use of multiple interventions, combined as appropriate according to the setting, malaria continues as a major public health problem. In areas of high transmission, malaria remains a major cause of child morbidity and mortality, even where insecticide treated net (ITN) coverage is high. This includes areas of highly seasonal transmission, where seasonal malaria chemoprevention (SMC) is provided monthly through the high transmission season. WHO estimated that in 2019, approximately 229 million cases and 409 000 deaths were attributable to malaria, with 94% of these deaths occurring in sub-Saharan Africa. Most malaria deaths in Africa occur in children younger than 5 years.[i] Most malaria deaths in Africa occur in children younger than 5 years. Furthermore, the last four WHO World Malaria Reports have indicated that progress in malaria control has stalled, with very little reduction in the past 5 years despite continued efforts to increase coverage and access to current interventions. In some sub-Saharan African countries, cases are increasing.[2] All of our current malaria control interventions are either insecticide or drug based, and are threatened by emerging resistance[3].	Notably, the malaria control situation is different than when the RTS,S vaccine was considered for by WHO in 2015. At that time, malaria cases had been declining year-on-year as a result of ITNs and introduction of highly effective artemisinin-containing therapy.

[2] World Malaria Report 2020. 2020, World Health Organization: Geneva, Switzerland
[3] Global plan for insecticide resistance management in malaria vectors. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/10665/44846/1/9789241564472_eng.pdf, accessed 10 March 2015)
WHO, Roll Back Malaria Partnership. Global plan for artemisinin resistance containment. Geneva: World Health Organization; 2011 (http://www.who.int/malaria/publications/atoz/artemisinin_resistance_containment_2011.pdf, accessed 10 March 2015

Evidence-to-recommendations framework: RTS,S/AS01 malaria vaccine

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No*	*Un-certain*	*Yes*	*Varies*	Modeled estimates from the Swiss TPH and Imperial College were updated in 2021 utilizing the underlying model structure and vaccine parameterization from the 2015 analysis and more comprehensive coverage and cost of delivery data that have been informed by MVIP. In moderate to high transmission settings, median predictions from the two models were 417 and 448 deaths averted per 100 000 fully vaccinated children (defined as having received at least 3 doses) and the range of model predictions at 80% level were 205-540 and 315-534 respectively. The models estimated 9.2% to 18.6% of all malaria deaths averted in vaccinated children < 5 years. Modest vaccine efficacy has potential translate into significant public health impact on morbidity and mortality. In large Phase 3 trial (2009-2014) participants who received 4-dose schedule at 5-17 months of age, vaccine efficacy (VE) against clinical malaria was 39% (95% CI 34.3,43.3) and VE against severe malaria up to the end of the trial was 31.5% (95%CI 9.3, 48.3). From month 0 to study end, 1774 cases of clinical malaria per 1000 children (95% CI 1387-2186; range across sites 205-6565) were averted.[4] This VE and impact observed were on top of existing interventions (i.e. insecticide treated nets) and was observed both where ITN use was high and in the two sites where ITN use was not high. Secondary objectives of the Phase 3 trial included the measurement of VE against severe malaria and against all-cause mortality. Vaccine efficacy against severe malaria was significant (as above), but because of the low mortality rate among children enrolled in the Phase 3 trial in which children had improved access to care, data derived from trials were insufficient to draw conclusions on of the impact of the vaccine on mortality. Extended follow up study (7-years follow-up total) of subset of children at 3 trial sites, showed that among trial participants given 4-dose and 3-dose schedules at 5-17 months, VE against severe malaria was 37% (95%CI15 to 53; p=0·0028) and 10% (95%CI −18, 32; p=0·44) respectively. VE against clinical malaria was 24% (95% CI: 16; 31) in 4-dose group and 19% (95% CI: 11; 27) in 3-dose group.[5] The evaluation of the Malaria Vaccine Pilot Implementation Programme in Ghana, Malawi and Kenya, after 2 years, demonstrated that high coverage of the vaccine was achieved, (in household surveys, 62% of children 12-23 months had received 3 doses of RTS,S/AS01 in Malawi, and 67% in Ghana; in	The SAGE and MPAG endorsed Framework for WHO Recommendation states that a WHO recommendation for broader use could be made in absence of data showing a vaccine impact on mortality. Impact on severe malaria is an acceptable interim surrogate indicator if assessed as consistent with a beneficial impact. The MVPE household survey showed equitable delivery of the RTS,S/AS01 vaccine with respect to gender, socio-economic status, and ITN use.
		☐	☐	☒	☐		

[4] RTS,S Clinical Trial 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): p. 31-45.

[5] Tinto, H., et al., 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): p. 821-832.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	Benefits of the intervention Are the desirable anticipated effects large? (continued from page 3)					Kenya, 69% had received 3 doses based on administrative data), and in pooled analysis of data from the three countries, introduction of RTS,S/AS01 was associated with a 30% reduction in the incidence of hospital admission with severe malaria (incidence rate ratio (IRR) 0.70, 95%CI 0.54, 0.92), a 21% reduction in hospitalization with a positive malaria test (IRR=0.79, 95% CI 0.68, 0.93), a 8% reduction in hospital admission for any cause (IRR=0.92, 95%CI 0.83, 1.03), and a 7% reduction in mortality due to any cause excluding injuries (IRR=0.93, 95% CI 0.84, 1.03). The impact on severe malaria was consistent with the impact that would be expected if the effectiveness of three doses of RTS,S/AS01 was equal to the efficacy observed in the Phase 3 trial, given the level of uptake of the vaccine in the pilot implementation. The 7% impact on mortality (not statistically significant) measured through the MVPE is consistent with what would be expected if malaria contributes to about 30% of deaths in young children. The household survey shows that the vaccine was provided equitably across socio-economic status and gender. Vaccine introduction did not negatively impact ITN use. Moreover, the vaccine improved equitable access to malaria control interventions, with 69-75% of children who did not sleep under an ITN the prior night having received at least one dose of RTS,S/AS01. In a 3-year study, conducted in settings of highly seasonal malaria, where seasonal malaria chemoprevention (SMC) is WHO-recommended as a highly efficacious means to reduce malaria during peak transmission season, trial participants were randomized to 3 arms; to receive SMC alone, to receive RTS,S/AS01 alone just before peak season with annual doses, or to receive SMC + seasonal RTS,S/AS01. At 3 years, a protective efficacy against clinical malaria of 62.8% (95% CI 58.4, 66.8) and 59.8% (95% CI 54.7, 64.0), were shown in the SMC + RTS,S/AS01 group compared with the SMC-alone or compared with the RTS,S/AS01 alone group, respectively. Importantly, RTS,S/AS01 alone provided seasonally was non-inferior to SMC alone.[6]	
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	In the large Phase 3 trial (2009-2014), one identified known safety risk was noted: febrile seizures within 7 days of vaccination and all cases resolved without sequalae. Three safety signals were identified, which were unexplained and without known causality: an excess of meningitis cases in RTS,S/AS01 recipients; an excess of cerebral malaria cases in a post-hoc analysis; and, also in a post-hoc analysis, an excess of deaths among girls who received RTS,S/AS01 but not among boys. In a 7-year follow-up study of a subset of children from three Phase 3 trial sites, no imbalance in safety signals was observed during the additional 3 years of follow-up. In addition, VE remained positive throughout the study period. In 2018, MPAC concluded these data provide further	

[6] Chandramohan et al, 2021. Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention. New England Journal of Medicine. https://www.nejm.org/doi/full/10.1056/NEJMoa2026330

	CRITERIA	JUDGEMENTS		RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	Harms of the intervention (continued from page 5)			reassurance on the absence of a rebound effect after dose 4 or of a persistent rebound effect after only 3 doses. This was based on the assessment that the previously observed apparent rebound of severe malaria among children who received only 3 doses of RTS,S/AS01 was time limited, with very few severe malaria cases after 4 years of follow up, and no further imbalance in safety signals or death and was seen as giving further reinforcement of the safety profile of the vaccine and its apparent benefit in children who receive either 3 or 4 doses. [7] The malaria vaccine pilot evaluation was well-powered when pooled across countries to detect adverse effects of the magnitudes observed in the Phase 3 trial if they occurred. -There was no evidence that RTS,S/AS01 introduction increased incidence of hospital admission with meningitis: incidence rate ratio (vaccinating: comparison areas) was 0.81 (95%CI 0.43, 1.55). -There was no evidence that RTS,S/AS01 introduction increased incidence of hospital admission with cerebral malaria: incidence rate ratio (vaccinating: comparison areas) was 0.77 (95% 0.44, 1.35). --There was no evidence that the effect of RTS,S/AS01 introduction on all-cause mortality differed between girls and boys: relative mortality ratio (the mortality ratio between vaccinating and comparator areas, for girls, relative to the mortality ratio for boys), was 1.08 (95%CI 0.93, 1.25). Further evidence on vaccine safety was obtained from the following studies, in which no malaria vaccine associated increase in meningitis, cerebral malaria or female deaths was observed: the Phase 3 trial of RTS,S/AS01 with SMC (N~6000, ~4000 children received RTS,S/AS01 dose 1)[6] and the Phase 3 fractional dose trial (N=1500; 1200 children received RTS,S/AS01 dose 1), or pooled Phase 2 RTS,S/AS clinical trials (N~2000).[8] Routine pharmacovigilance in the 3 pilot countries, where over 2 million doses of RTS,S/AS01 have been administered through the routine EPI clinics, and over 710 000 children have received at least 1 RTS,S/AS01 vaccine dose, did not show an imbalance in the safety signals identified in the Phase 3 trial, nor did it reveal any new safety signals. The European Medicines Agency (EMA) has maintained a positive scientific opinion under article 58, stating that benefits outweigh risks and the vaccine has an acceptable safety profile.[9] Data from the pilot and other studies listed support the EMA conclusion that the safety signals observed in the Phase 3 trial were likely chance findings.	

[7] Framework for Recommendation on RTS,S, April 2019: https://www.who.int/malaria/mpac/proposed-framework-for-policy-decision-on-rtss-as01-malaria-vaccine.pdf

[8] Vekemans, J., et al., *Pooled analysis of safety data from pediatric Phase II RTS,S/AS malaria candidate vaccine trials.* Hum Vaccin, 2011. **7**(12): p. 1309-16.

[9] *Mosquirix: Opinion on medicine for use outside EU*. [cited 2021 July 1]; Available from: https://www.ema.europa.eu/en/mosquirix-h-w-2300.

Evidence-to-recommendations framework: RTS,S/AS01 malaria vaccine

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	Balance between benefits and harms	*Favours inter-vention* ☒ *Favours com-parison* ☐ ~~*Favours both*~~ *Favours neither* ☐ *Unclear* ☐	In the large Phase 3 trial, the vaccine was shown to protect against clinical and severe malaria, severe malaria anemia, blood transfusions, hospitalization due to malaria, and all-cause hospitalizations. Benefits against malaria-related mortality and all-cause mortality are unknown, but severe malaria is a sufficient proximal marker of malaria mortality. In pilot introductions, with vaccine provided through the routine system, relatively high coverage levels of the first 3 vaccine doses were obtained over a relatively short period and during the Covid-19 pandemic (surveys assessed coverage of 3 doses in children 12-23 months as 62% in Malawi and 67% in Ghana . During the first 24 months of vaccine introduction, a statistically significant 30% reduction in hospitalized severe malaria and a 21% reduction in hospitalization with malaria was observed. There was no indication of a reduction in use of ITNs or a change in health seeking behavior or diagnosis and treatment of febrile illness was observed with malaria vaccine introduction. The vaccine is generally well-tolerated, with an identified risk of febrile convulsions within 7 days of vaccination. The MVPE was well powered to detect the safety signals of the magnitude observed in the Phase 3 trial. The safety signals observed during Phase 3 trial were not observed in the pilot implementations. No additional concerns were raised through the routine national pharmacovigilance, the Phase 3 post-authorization safety analysis by GSK, the trial of seasonal RTS,S/AS01 with or without SMC, nor the pooled Phase 2 trial safety analysis. Concerns about potential excess risk of severe malaria should a child not receive dose 4 were not borne out in the extended follow-up study of 3 sites in the Phase 3 trial, in the modeling study, nor in re-assessment of the Phase 3 trial data, which showed reductions in severe malaria among children who received 3 vaccine doses prior to the end of the Phase 3 trial.	*2019 Framework:* Recommendation on use of RTS,S/AS01 could be made if and when: - concerns regarding safety signals observed in the Phase 3 trial (related to meningitis, cerebral malaria, and sex-specific mortality) satisfactorily resolved - either severe malaria or mortality data trends are assessed as consistent with a beneficial impact of the vaccine; *2019 Framework:* WHO recommendations for broader use of RTS,S need not be predicated on attaining high coverage (including coverage of dose 4). The overall benefit/risk in context of what can be implemented is positive. Judgment options defined by the Working Group as: - "Favours intervention:" RTS,S/AS01 plus other malaria control interventions - "Favours comparison" other malaria control interventions - "Neither" intervention nor the control are acceptable - "Unclear" if either intervention or control are acceptable

Evidence-to-recommendations framework: RTS,S/AS01 malaria vaccine

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Mod-erate* ☐ *High* ☒ Safety of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Mod-erate* ☒ *High* ☐	The certainty of the evidence ranged from very low to high; however, most outcomes have been rated as either **moderate or high certainty**.	The main reason for downgrading the certainty of the evidence was imprecision, mostly for safety outcomes, due to the small number of events. In the Phase 3 trial there were 22 cases of meningitis; 53 cases of cerebral malaria; 156 deaths in girls, and 150 deaths in boys (notably far fewer than included in the analysis for the MVPE). The safety signals observed in the Phase 3 trial were rare, unexplained events. A significant risk difference was observed for meningitis following vaccination, but the causal relationship remained uncertain, with no clear causality model -the excess in meningitis cases in vaccinated children was seen only in the older age category (5-17 months at first vaccination), and not the younger age-category; there was no temporal relationship with vaccination, with cases occurring more than 1000 days after first vaccine dose; clustering of meningitis cases occurred by site, with 64% of cases from only 2 of the 11 sites (both outside of the meningitis belt); and, there was inconsistency in etiology, with cases of bacterial, mycobacterial, viral, and those with no pathogen isolated. It was also unclear whether the imbalance of cerebral malaria cases (in the setting of reduced severe malaria, of which cerebral malaria is a subset), or the excess mortality in vaccinated girls compared with boys seen in the trial were due to the vaccine, or were more likely chance findings. None of the safety signals were seen in the pooled safety analysis from Phase 2 trials (N ~ 2000, Vekemans et al).

Desirable	Study	Effect	Certainty
Clinical malaria	Phase 3 trial –RTS,S vs control Chandramohan - RTS,S vs SMC Chandramohan - RTS,S + SMC vs SMC Pilot Evaluations (MVPE) - RTS,S vs control	Favours RTS,S No difference Favours RTS,S + SMC Not reported	High High High -
Severe malaria	Phase 3 trial –RTS,S vs control Chandramohan - RTS,S vs SMC Chandramohan - RTS,S + SMC vs SMC MVPE – RTS,S vs control	Favours RTS,Ss No difference Favours RTS,S + SMC Favours RTS,S	High Low Moderate Moderate
Severe malaria anaemia	Phase 3 trial – RTS,S vs control Chandramohan[a] -RTS,S vs SMC Chandramohan - RTS,S + SMC vs SMC MVPE – RTS,S vs control	Favours RTS,S No difference Favours RTS,S + SMC Not reported	Moderate Low Moderate -
Blood transfusion	Phase 3 trial – RTS,S vs control Chandramohan - RTS,S vs SMC Chandramohan - - RTS,S + SMC vs SMC MVPE – RTS,S vs control	Favours RTS,S No difference Favours RTS,S + SMC Not reported	Moderate Low Moderate -
Hospital admission	Phase 3 trial – RTS,S vs control Chandramohan - RTS,S vs SMC Chandramohan - RTS,S + SMC vs SMC MVPE – RTS,S vs control	Favours RTS,S No difference No difference No Difference	High Low Low Moderate
Undesirable			
Cerebral malaria	Phase 3 trial – RTS,S vs control Chandramohan - RTS,S vs SMC Chandramohan[b] - - RTS,S + SMC vs SMC MVPE – RTS,S vs control	Favours comparison Probably no diff 4 vs 0 events Probably no diff 1 vs 0 events No difference	Very low Low Low Moderate
All-cause mortality	Phase 3 trial – RTS,S vs control Chandramohan[a] - RTS,S vs SMC Chandramohan[b] - RTS,S + SMC vs SMC MVPE – RTS,S vs control	Girls - Favours comparison Boys - No difference Girls - No difference Boys - No difference Girls - No difference Boys - No difference Girls - No difference Boys - No difference	Low Low Low Low Moderate Moderate Moderate Moderate
Meningitis	Phase 3 trial – RTS,S vs control Chandramohan[a] - RTS,S vs SMC Chandramohan[b] - RTS,S + SMC vs SMC MVPE – RTS,S vs control	Favours comparison No cases in either group No cases in either group No difference	Low Low Low Moderate

Evidence-to-recommendations framework: RTS,S/AS01 malaria vaccine

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☐ | *No important uncertainty or variability* ☒ | *No known undesirable outcomes* ☐	In the MVIP, severe malaria was reduced by 30% during the first 24 months of vaccine introduction, when the vaccine was delivered by the MoH through the routine childhood immunization programme, achieving high impact in a real-life situation on top of current malaria control interventions. Hospitalization with malaria infection was reduced by 21%. Additionally, the Phase 3 trial conducted between 2009 and 2014 demonstrated a 40% reduction in malaria cases presenting at the health facility or hospital. The seasonal malaria vaccination trial[6] showed how vaccine delivery can be optimized for higher efficacy and impact. Undesired effects include risk of febrile convulsions; reactogenicity - including fever after vaccination; and the requirement to administer a 4-dose schedule requiring new vaccine visits* Caregiver and health worker interviews and statements from the MoH in the pilot countries indicate that the relative importance of the desirable outcomes over the undesirable outcomes is high.	Malaria remains a primary cause of childhood death in sub-Saharan Africa, with financial and societal repercussions. High value placed on reduction of uncomplicated and severe malaria, and malaria death. *Notably, most, if not all sub-Saharan African countries, recommend monthly child health visits until 5 years of age, so these should not be new health facility visits.
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | *Varies* ☐	All 3 MVIP countries showed increasing utilization (coverage) of the vaccine, captured through both administrative and survey data, over 24-months of RTS,S/AS01 implementation. Midline household surveys estimated coverage rates of 79.7%, 79.5%, and 74.1% for dose 1 and 71.2%, 65.5% and 65.2% for dose 3, respectively for Ghana, Kenya, and Malawi (measured through available immunization cards). Survey results were consistent with coverage estimates from the administrative data and suggest acceptability by target population, caregivers, and health workers administering the vaccine. Midline surveys did not find any significant difference in vaccine coverage by the child gender, socio-economic status, or ITN use. These data indicate relatively rapid scale up for a new vaccine with a unique schedule; dropout between doses has been comparable to other vaccines. A qualitative study (HUS) conducted within the MVIP found the following: --Severity and frequency of malaria widely recognized among primary caregivers who expressed strong enthusiasm for a malaria vaccine regardless of individual concern/question about RTS,S --In all countries, uptake of RTS,S/AS01 doses 1-3 generally high, initially (dose 1) based on strong trust in government, health system, and vaccines and later (doses 2-3) shifting to specific trust in RTS,S/AS01 as caregivers observe absence of side effects and perceive direct benefits of the vaccine (malaria less frequent and severe). --When adequately informed about dose schedules, caregivers are motivated to attend additional visits for vaccinations, including RTS,S/AS01.	Household survey and administrative data from the MVPE indicate the value of vaccine and acceptability by target population, with relatively rapid scale up for a new vaccine with a unique schedule, and dropout between doses comparable to other vaccines. HUS data indicate high acceptance and desirability of the vaccine. Midline surveys and the second round of the qualitative study were conducted between provision of dose 3 and dose 4 and thus did not capture data on the uptake/coverage/ acceptability of dose 4.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
						--Almost all caregivers whose children received 3 RTS,S/AS01 doses were aware of dose 4 at 24 months and expressed commitment to taking the child. Post introduction evaluation (PIE) conducted in Malawi (non-representative sample) found that 83% of community members accepted the vaccine; 89% of community members were aware the vaccine provides partial protection and 83% were aware of potential side effects, such as fever.	
RESOURCE USE	Are the resources required small?	*No*	*Un-certain*	*Yes*	*Varies*	Additional resources are required for commodity procurement and for the health system provision of the new vaccine. Additional health system resources will be required for adding new vaccination visits (at least 1 for first 3 doses and additional visit for dose 4). The MVIP cost of delivery study found: Incremental non-vaccine cost of introducing and delivering a dose of RTS,S/AS01 ranges between $1.20-$2.50 (financial) and $2.07-$4.77 (economic) across MVIP countries. Cost of delivery is slightly lower if considering the first 3 doses, (range: $0.94- $1.97 (financial); $1.71-$3.86 (economic). Cost of delivery is likely slightly higher for dose 4: there is limited data to infer cost of delivery of dose 4 at the time of this analysis. Although not directly comparable, MVIP cost of delivery estimates are broadly consistent with previous cost projections of RTS,S/AS01 delivery[10,11]. The resources needed to deliver RTS,S/AS01 may be generally comparable with other new vaccines. The cost estimates of RTS,S/AS01 delivery during the pilot is relatively higher than the cost per dose for newly introduced vaccines such as PCV or Rotavirus $0.84 (range: $0.48 to $1.38, economic)[12], but comparable with the HPV vaccine pilot implementation which range between $1.74 and $2.24 (financial) and between $2.22 and $4.29 (economic).[8] Comparisons of the MVIP costing estimates to findings from the literature should be made cautiously, acknowledging that the methods and the delivery strategies are different, and these estimates are drawn from ongoing pilot studies rather than a full national introduction. GSK has committed to at-cost (plus 5%) pricing for the vaccine. GSK has also a product transfer agreement with Bharat Biotech Industries Ltd; the stated intention of this product transfer is to ensure the long-term, low-cost production of RTS,S.	Resources may not be small, but modelling indicates highly cost effective at US$ 5-10 per dose (other cost effectiveness studies had different costs associated). Resources required are likely comparable with other new vaccine introductions. Resource requirement is largely dependent on vaccine price and potential donor funding available to support vaccine purchase and introduction. The added benefit provided through the ability of the malaria vaccine to reach children not currently accessing ITNs or other malaria preventive measures should be considered. Likewise, the relatively rapid scale up to coverage levels that are higher than those reached for most other malaria interventions, and the delivery through an established platform are unique features for a malaria intervention that should be considered as part of the cost assessment and when considering the value of the vaccine. There are implied costs of vaccine introduction however the size of resources required depends on perspective and cost effectiveness. The magnitude is likely to vary depending how countries in sub-Saharan Africa integrate the vaccine within the available vaccine portfolio, malaria control efforts, and multiple other factors.
		☒	☐	☐	☒		

[10] Galactionova K, Bertram M, Lauer J, Tediosi F. Costing RTS,S introduction in Burkina Faso, Ghana, Kenya, Senegal, Tanzania, and Uganda: A generalizable approach drawing on publicly available data. Vaccine 2015; 33:6710–6718.
11 Sicuri E, Yaya Bocoum F, Nonvignon J, et al. The Costs of Implementing Vaccination With the RTS,S Malaria Vaccine in Five Sub-Saharan African Countries. MDM Policy Pract 2019; 4.
[12] Immunization Delivery Cost Catalogue. http://immunizationeconomics.org/ican-idcc-findings#anchor-top

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	Cost-effectiveness	*No*	*Un-certain*	*Yes*	*Varies*	Predictions of RTS,S/AS01 cost-effectiveness per disability-adjusted-life year (DALY) averted are comparable with other new vaccines. In 2015, four mathematical models of the impact of RTS,S/AS01 predict a substantial additional public health impact in settings with prevalence of infection in those aged 2-10 years between 10% and 65%.[13] Predictions from two of the four models (Imperial College and Swiss TPH) were subsequently fit against the results on severe malaria from the follow up study in three of the Phase 3 trials sites. The model predictions were found to be consistent with the measured impact of the from the longer-term follow up study, supporting the validity of the earlier cost effectiveness estimates. Predictions from the Swiss TPH and Imperial College were updated in 2021 utilizing the underlying model structure and vaccine parameterization from the 2015 analysis and more comprehensive coverage and cost of delivery data that have been informed by MVIP. In moderate to high transmission settings, median predictions from the two models were 417 and 448 deaths averted per 100 000 vaccinees in a 4-dose schedule (where a fully vaccinated child is defined as any that has received at least 3 doses) , and the range of model predictions at 80% level were 205-540 and 315-534 respectively. The two models estimated 9.2% to 18.6% of all malaria deaths averted in vaccinated children < 5 years. Modelling predictions indicate a significant public health impact and high level of cost-effectiveness in those settings if implemented after achieving high bed net usage and high coverage of SMC, where latter intervention is appropriate. Predictions using the Swiss TPH model, at a price of $5 per dose, predicted the median cost-effectiveness ratio of $97 (range $81-$230) per DALY averted in various African countries. Predictions using the Imperial College model predicted the median cost-effectiveness ratio of $103 (range $86 - $151) per DALY averted at a price of $5 per dose program cost. Although summary statistics from the 2015 and 2021 analyses are not directly comparable, the cost per DALY averted and cost per clinical case averted predictions marginally increased based on the updated additional cost of delivery predictions. Central estimates of cost-effectiveness from individual models still fall within the range of those presented in 2015 and RTS,S/AS01 is still predicted to be cost-effective compared with standard norms and thresholds. This result suggests that RTS,S/AS01, conditional on assumptions on price, coverage, and vaccine properties, is highly cost-effective across African countries.	The 2019 Framework for WHO recommendation states: Cost-effectiveness estimates should be regularly refined as data become available for increasingly precise calculations and presented at appropriate time points. The anonymized six African country analysis of CEA done in 2015 suggest the cost effectiveness of RTS,S introduction range between $92 - $282 per DALY averted across countries. These results are consistent with that observed in the transmission setting specific estimates.[14]
		☐	☐	☒	☐		

[13] Penny, M.A., et al., Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. Lancet, 2016. 387(10016): p. 367-375.

[14] Galactionova K, Bertram M, Lauer J, Tediosi F. Costing RTS,S introduction in Burkina Faso, Ghana, Kenya, Senegal, Tanzania and Uganda: a generalizable approach drawing on publicly available data. Vaccine. 2015;33(48):6710–8

Evidence-to-recommendations framework: RTS,S/AS01 malaria vaccine

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
EQUITY	What would be the impact on health inequities?	*Increa-sed*	*Un-certain*	*Re-duced*	*Varies*	Household surveys in Ghana and Malawi showed that vaccine uptake was equitable, with similar coverage across socio-economic groups and in boys and girls. Vaccine introduction did not negatively impact ITN use, uptake of other childhood vaccines, or health seeking behavior. Introduction of the vaccine resulted in broadened access to at least one malaria preventive intervention (ITNs or malaria vaccine). Data from the household surveys (reflecting the first 18-20 months of vaccine introduction) show that the availability of the malaria vaccine expanded the reach of malaria preventive interventions to vulnerable children. In Ghana 69% of children reportedly slept under an ITN the night prior to the survey and 77% had received a first dose of RTS,S/AS01. Among children who did not sleep under an ITN, 72% received a first dose of the malaria vaccine. The introduction of the malaria vaccine expanded the percentage of children accessing at least one malaria prevention measure – an ITN or the malaria vaccine - from 69% to 91%, while 55% of children benefitted from both an ITN and the vaccine. Similar results were observed in Malawi, where ITN use was 67%, vaccine coverage was 79%, and among the children who did not sleep under an ITN, 75% were vaccinated with the malaria vaccine. The introduction of the malaria vaccine expanded the uptake of at least one malaria preventive intervention from 67% of children to 92%, with 54% benefiting from both interventions. In Kenya, reported ITN use was very high, at 92%, malaria vaccine coverage was 79% and among children who did not sleep under an ITN the prior night, 69% received the first malaria vaccine dose. The addition of the malaria vaccine resulted in 97% of children accessing at least one malaria preventive intervention, with 73% of children benefiting from both interventions.	**This criteria was considered in context of following questions:** Is the condition more common in certain disadvantaged group? • *Children under 5 years are most affected by malaria, pronounced in the rural and poor (low SES) populations (World Malaria Report. 2020)* Is its severity greater, in people from specific group or with a particular disability? • *Exposure to HIV and HIV infection has direct or indirect role on child health outcomes – malaria, anemia and nutrition (Dorsey G, et al ; Malaria J, 2012, Berkley et at 2009 and Hendrikensen et at 2012)* • *Chronic malnutrition is associated with severity of malaria (Das D, et al BMC 2018)* • *Malnutrition and being female was associated with increased mortality in children aged less than 10 years (Tshimanga M, et al, Pan Afr Med J 2017)* • *The vaccine has been shown to be safe and efficacious in malnourished children (MAL 055 clinical trial data) and in HIV infected children (Otieno, L et al, Lancet Infect Dis 2016)* • *Homozygous sickle cell disease does not confer protection for severe malaria* Are there significant differences resulting in varying levels of access to intervention or coverage levels? Is there a risk that discrimination could impact outcomes? • *In some (but not all) countries, access to malaria control measures differ by SES, rural/urban settings (WMR, 2020)*
		☐	☐	☒	☐		

Evidence-to-recommendations framework: RTS,S/AS01 malaria vaccine

	CRITERIA	JUDGEMENTS					RESEARCH EVIDENCE	ADDITIONAL INFORMATION
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health (MoH), Immunization Managers)?	*Inter-vention* ☒	*Com parison* ☐	~~*Both*~~	*Neither* ☐	*Un-clear* ☐	MoH, through the support of the MVIP, promoted use of RTS,S/AS01 in the vaccine implementation areas. Other malaria preventive measures were supported by the MoH in all MVIP areas. The Malawi PIE conducted in mid-2021 (not necessarily representative samples) reported that: 100% of health workers accepted RTS,S/AS01 as an addition to the available vaccine portfolio and malaria intervention tools, 83% of district level respondents stated that the introduction of RTS,S/AS01 improved the routine immunization programs. 67% of health sector respondents said the introduction of malaria vaccine was successful; 57% said that vaccine introduction improved the EPI. Good uptake and coverage of the malaria vaccine (as noted through the administrative data and the household survey) provide further evidence of acceptability by MOH staff administering the vaccine. Health providers interviewed through the qualitative HUS study expressed positive perceptions of the vaccine as an intervention and a significant component of malaria control efforts. Consistent with findings from primary child caregivers, health providers also emphasized the positive responses from the caregivers and perceptions about the vaccine's benefits. Chief concerns from health providers were around operational challenges faced in introducing and delivering RTS,S/AS01 (i.e. increased workload, training, eligibility). The vaccine itself was not the subject of questions or challenges, suggesting antigen itself continues to be acceptable to providers.	Judgment options defined as: - "Intervention:" RTS,S/AS01 plus other malaria control interventions is an acceptable option - "Comparison" other malaria control interventions is only acceptable option - "Neither" intervention nor the control are acceptable - "Unclear" if either intervention or control are acceptable - Note: "Both" removed due to lack of clarity in meaning MVIP countries (Ghana, Kenya, and Malawi) have valuable lessons learned and guidance based on their experiences implementing the MVIP vaccine when it comes to vaccine launch, stakeholder engagement, communications, schedule considerations, and integration within existing MoH programmes. Coordination between the NMCP and EPI programmes at central, regional and local levels were considered important for successful implementation.
	Which option is acceptable to target group?	*Inter-vention* ☒	*Com parison* ☐	~~*Both*~~	*Neither* ☐	*Un-clear* ☐	The MVIP midline survey found no impact on use of ITN in intervention areas following introduction of RTS,S/AS01—indicating both interventions are acceptable. Overall health seeking behavior for febrile illnesses was also found to be similar between intervention and comparison groups and between baseline and midline surveys. Good uptake and coverage (as noted through administrative data and household survey) provide further evidence of acceptability; modest drop-out rate and continued increases in uptake suggest that additional visits are seen as acceptable to target populations. Within the MVIP qualitative study, malaria was seen by the population as a significant health risk and RTS,S/AS01, together with other malaria control measures, was seen as an acceptable intervention. Caregivers perceived the vaccine as reducing the severity and frequency of malaria. Positive attitudes and trust among caregivers increased substantially between R1 and R2 interviews, driven mainly by their perception of vaccine's health benefits in their own children and the broader community. Early concerns about safety were replaced by widespread perception that adverse events following immunization (AEFI) are "normal" and similar to other vaccines. Most caregivers expressed their intent to take their children to receive dose 4, and many did so enthusiastically.	Judgment options defined as: - "Intervention:" RTS,S/AS01 plus other malaria control interventions is an acceptable option - "Comparison" other malaria control interventions is only acceptable option - "Neither" intervention nor the control are acceptable - "Unclear" if either intervention or control are acceptable - Note: "Both" removed due to lack of clarity in meaning

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	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | *Varies* ☐	As of June 2021, more than 2.1 million doses of RTS,S/AS01 had been administered and more than 740 000 children across Ghana, Kenya, Malawi had received dose 1 through childhood vaccination using the strategies routinely used for new vaccine introduction. Demand and uptake of all doses has been strong in all three countries despite the challenges brought about by the COVID-19 pandemic. While there was variation in performance observed, according to administrative data, all three countries reached at least 74% of their target populations with RTS,S/AS01 dose 1 and at least 63% with the RTS,S/AS01 dose 3. This level of uptake is considered satisfactory and within expectations for a new vaccine with a novel schedule, i.e. targeting children as of 5 months (in Malawi) and 6 months (Ghana and Kenya) for dose 1. Administrative data indicate that dose 4 can reach children, with drop out between dose 3 and 4 at approximately 19% in Malawi and 31% in Ghana after approximately 9 months of introduction of dose 4. This level of drop out early after vaccine introduction is not unexpected. It is not yet known whether additional efforts will be needed to increase dose 4 uptake. Data on the perceptions and utilization of dose 4 from the qualitative study is currently pending and will provide a clearer reflection on the feasibility of the 4-dose schedule. However, qualitative interviews with health providers and other sub-national health sector staff, supported by evidence from child caregivers, suggest that with time, a 4-dose RTS,S/AS01 schedule is feasible to implement: Providers have positive attitudes about RTS,S/AS01 and perceive that child caregivers value it as well. Understanding of dose eligibility has generally improved over time, likely reflecting improved training materials and increased familiarity with the vaccine. This finding is consistent with improved understanding of eligibility among child caregivers.	Regarding RTS,S/AS01 provided seasonally, there is no programmatic evidence at this point in time to understand whether the seasonal vaccine administration is feasible. Other malaria control interventions have been provided intermittently, (SMC, Intermittent Preventive Treatment of malaria in infancy (IPTi), Intermittent Preventive Treatment of malaria in pregnancy (IPTp), indoor residual spraying (IRS). Administration mechanisms differ between these interventions and differ to vaccine administration. *2019 Framework:* Need not be predicated on attaining high coverage (including dose 4). High coverage frequently not attained until several years after start of implementation.

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☒
Type of recommendation	We recommend the intervention ☒	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations	We recommend the comparison ☐	We recommend against the intervention and the comparison ☐	
Recommendation (text)	**The RTS,S SAGE/MPAG Working Group recommends that RTS,S/AS01 should be provided at a minimum of 4 doses to reduce malaria disease and burden in children from 5 months of age living in countries in sub-Saharan Africa with moderate to high malaria transmission.** The RTS,S/AS01 vaccine has an acceptable safety profile, and its introduction results in a significant reduction in severe malaria, an acceptable surrogate indicator for the likely impact on mortality. The Working Group notes that the vaccine provides substantial added protection against malaria illness and death even when provided in addition to a package of existing interventions which are known to reduce the malaria burden. The introduction of a vaccine at this time would come when progress in recent years has stalled in malaria control in Africa, when our current tools are threatened by drug and insecticide resistance, and when malaria remains a primary cause of illness and death in African children, with more than 260 000 child deaths from malaria annually.				

Recommendation (continued)	In areas of moderate to high, perennial malaria transmission, the vaccine should be provided as a 3-dose primary series, starting from around 5 months of age and with a minimal interval between doses of 4 weeks. For children who are delayed in receiving dose 1, vaccination should be started before 18 months of age. A dose 4 should be given between about 12 and 18 months after dose 3 (i.e., at around 18 months to 2 years of age), however there can be flexibility to optimize delivery. The minimal interval between doses 3 and 4 should be 4 weeks. In areas with highly seasonal malaria or areas with perennial malaria transmission with seasonal peaks, the RTS,S SAGE/MPAG Working Group recommends that consideration should be given to the option of providing the RTS,S/AS01 vaccine seasonally, with potential 5-dose strategies including: 1) For all children under 5 years of age who have already completed the 3-dose primary series through routine administration, provide annual dose(s) just prior to the peak transmission season, or 2) For all children 5-17 months of age, give the 3-dose primary series monthly as a "campaign" just prior to the peak transmission season and then in subsequent years provide an annual dose just prior to peak seasons. The RTS,S SAGE/MPAG Working Group makes this recommendation for possible 5-dose seasonal malaria vaccination strategies based on available data. The Working Group understands that this trial is continuing with additional doses provided to children up until the age of 5 years, and final results will contribute evidence on vaccine efficacy beyond 5 doses. The Working Group also notes that providing dose 1 from 5 months of age may limit opportunities for integration with the delivery of other vaccines and/or for protection of children slightly younger (i.e., 4 months). The Working Group notes that the careful and intentional monitoring for the safety signals seen in the Phase 3 trial, through quality data collection at sentinel hospitals and through community-based mortality surveillance, has revealed no evidence that the safety signals observed in the Phase 3 trial were causally related to the RTS,S/AS01 vaccine. Thus, the Working Group does not recommend special mechanisms be put in place to look for these signals during expansion of vaccine use or adoption by other countries. WHO should lead the development of a Framework to guide where the initial limited doses of a malaria vaccine should be allocated, through a transparent process that incorporates input by key parties, with appropriate representation and consultation. This Framework should include dimensions of market dynamics, learning from experience, scientific evidence for high impact, implementation considerations, and social values, including fairness, and equity. The MVIP should continue as previously planned for an additional two years to 1) measure the impact of the introduction of RTS,S/AS01 on mortality; and 2) measure the added benefit of dose 4 (the Working Group noted that in the Phase 3 clinical trial, the impact on severe malaria was only seen among children who had received 4 doses of the vaccine but there was impact on clinical malaria among children who received only 3 doses, though lower than that observed on children who had received 4 doses). Data collection on severe malaria and safety endpoints should continue. Any revisions or modifications concerning the recommendation for dose 4 can be made at the end of the pilots.

Implementation considerations	• Flexibility in dosing schedules is encouraged. Countries may want to provide dose 1 slightly earlier than 5 months of age and may want to provide the first 3 doses monthly. The pilot uncovered situations where the 6,7,9 month schedule caused some confusion. Likewise, MoH officials have expressed an interest in providing dose 4 at the same time as the meningococcal A (MenA) conjugate vaccine or the second dose of measles and rubella (MR), e.g. both at 18 months of age. • Data on seasonal vaccination supports its use in the Sahel and sub-Sahel region, and it may be appropriate for areas outside of the Sahel region where malaria transmission varies substantially by season. A seasonal strategy may optimize vaccine efficacy in other areas with moderate to high transmission and seasonality. • Vaccination should continue in the MVIP areas implementing RTS,S/AS01, and expand to the pilot evaluation comparison areas as soon as feasible.
Monitoring and evaluation	• Data from the MVPE and other studies show no evidence that the safety signals observed in the Phase 3 trial were causally related to the RTS,S/AS01 vaccine. Strengthening of national pharmacovigilance systems is highly desirable to detect unanticipated adverse effects of this vaccine and any other newly introduced vaccines, as well as for vaccines already in use. • MVIP will continue to monitor for or collect data on safety and impact, and on the value of dose 4, through to the end of the programme and in the planned case control study. • Based on experience in the three pilot countries, the MVIP will also provide information on how best to achieve coverage of dose 4. • Monitoring and evaluation around flexible schedules and implemented strategies are encouraged; this includes strategies for seasonal vaccination of RTS,S/AS01. • Vaccine effectiveness studies following widespread introduction.
Research priorities	The following research are recommended for the following areas, with the Working Group noting that none are prerequisite prior to expanded use of RTS,S/AS01. 1. Areas with moderate to high malaria transmission with perennial transmission: • Through the MVIP, continued collection and monitoring data on safety and impact through the end of the programme and in the planned case control study. • Through the MVIP, collect additional information on how best to achieve coverage of dose 4, and its impact on severe malaria and mortality. • Added or synergistic effect of RTS,S/AS01 when given in conjunction with expanded IPTi. 2. Areas with highly seasonal malaria or areas with perennial malaria transmission with seasonal peaks: • Operations research around the delivery of seasonal vaccine dosing, including around annual pre-season dosing after a primary series given through the routine health clinics. • Further evaluation to determine how best to deliver the combination of SMC and seasonal malaria vaccination in areas of high malaria burden in the Sahel, sub-Sahel, and areas of perennial transmission with seasonal peaks.

Research priorities (continued)	• Safety, immunogenicity, and effectiveness of annual doses beyond dose 5. • Planned follow-up of the ongoing seasonal malaria vaccination trial and case-control study, and evaluation of any age shift effect of clinical or severe malaria cases in immunized children (relative to the control group) after ceasing vaccination. 3. Both areas (1) and (2): • Parasite genotype monitoring to detect any emergence of vaccine escape mutants – in context of broader use of RTS,S/AS01 • Co-administration of RTS,S/AS01 with typhoid conjugate, Meningococcal, and inactivated polio vaccines, and other antigens as appropriate.

Annex 9c: Risk of bias assessment (for studies included in GRADE)

Author(s): Villanueva G, Henschke N, Hamel C, Buckley B (Cochrane Response)

[1]RTS,S Clinical Trials Partnership -2015

1. RTS, S Clinical 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. The Lancet; 2015.

ROB Domain	Judgement	Text supporting judgement
1. Was the allocation sequence adequately generated?	Low risk	In supplementary appendix: "Participating children from each age category were randomized into one of three study groups according to a 1:1:1 ratio (R3R, R3C or C3C) using a randomization algorithm with SAS version 9.1."
2. Was allocation adequately concealed?	Low risk	The treatment allocation at the investigator site will be performed using a central randomization system on Internet (SBIR).
3. For cluster RCTs, was there bias arising from the timing of identification and recruitment of participants? (see Figure 1)	n/a	Participants were individually randomized.
4. Was knowledge of allocated intervention adequately prevented during study? (i.e., blinding of participants and personnel)	All outcomes: Low risk	"Data were collected in a double-blinded (observer-blind) manner; the vaccinated children and their parent(s)/guardian(s) as well as those responsible for the evaluation of study endpoints were unaware of whether RTS,S/AS01 or a comparator vaccine had been administered to a particular child. The vaccines used in this study were of different appearance. The content of the syringe was, therefore, masked with an opaque tape to ensure that parent(s)/guardian(s) were blinded. The only members of study staff who knew of the vaccine assignment were those responsible for preparation and administration of vaccines; these staff played no other role in the study except screening or collection of biologic specimens."
5. Was knowledge of allocated intervention adequately prevented during the study from outcome assessors?	All outcomes: Low risk	See above.

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ROB Domain	Judgement	Text supporting judgement
6. Were incomplete outcome data adequately addressed?	All outcomes except AEs: Low risk	A modified ITT analysis was used which included all children who received at least one dose.
7. Are reports of the study free of suggestion of selective reporting?	Low risk	There are 65 outcomes listed in the trial registry. All the results are reported in the trial registry.
8. Was the study apparently free of other problems that could put it at high risk of bias?	Unclear risk	The study was funded by GSK, the manufacturer of the interventional vaccine. "GSK Biologicals SA were involved in the study design, and coordinated data collection, data analysis, data interpretation, and writing of the report."
Outcomes: Clinical malaria, Severe malaria, Anemia, Blood transfusion, Hospital admission, All-cause mortality, Safety	**Overall risk**: Low risk	No details on allocation concealment and heavy involvement of the funder within the project.

Domains highlighted in blue are outcome specific.

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[2]Chandramohan 2021

2. Chandramohan D, Zongo I,Sagara I,Cairns M,Yerbanga RS,et al. Seasonal malaria vaccination with or without seasonal malaria chemoprevention. New England Journal of Medicine; 2021.

ROB Domain	Judgement	Text supporting judgement
1. Was the allocation sequence adequately generated?	Low risk	Children were allocated randomly by an independent statistician. "The randomization list used permuted blocks after sorting by age, gender, area of residence and prior receipt of chemoprevention."
2. Was allocation adequately concealed?	Low risk	"Tablet PCs with the randomization list were accessible only to the chief pharmacist."
3. For cluster RCTs, was there bias arising from the timing of identification and recruitment of participants? (see Figure 1)	n/a	Individually randomized
4. Was knowledge of allocated intervention adequately prevented during study? (i.e., blinding of participants and personnel)	Low risk	The study registry (NCT03143218) states that it is triple blind (participant, care provider, investigator). "Syringes containing study vaccines were prepared by a chief pharmacist and masked with tape to blind the vaccine administrator, caretakers and children to the vaccine being given. The pharmacist and the vaccine administrator took no further part in the trial." "Drugs were pre-packaged by a pharmacist, who took no further part in the trial, in re-sealable enveloped labelled with the QR code. Each dose of SP+AQ or placebo was administered as directly-observed therapy by project staff at distribution points in study villages."
5. Was knowledge of allocated intervention adequately prevented during the study from outcome assessors?	Low risk	"All other investigators and study staff remained blind to treatment allocation."
6. Were incomplete outcome data adequately addressed?	Low risk	6861 children were randomized with 5920 children (86.3%) receiving at least one dose of study vaccine (no difference between the 3 groups).

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ROB Domain	Judgement	Text supporting judgement
		"The primary analysis was by modified ITT. The mITT population included all eligible children whose parents consented and who received a first dose of study vaccine in April 2017." "Secondary outcomes were analysed only by mITT."
7. Are reports of the study free of suggestion of selective reporting?	Unclear risk	There are 14 outcomes reported in the trial registry. All primary and secondary outcomes are reported in the main report or supplementary appendix.
8. Was the study apparently free of other problems that could put it at high risk of bias?		The study registry was first posted on May 8, 2017 however the study began on April 17, 2017. Although this was retrospectively registered (by ~3 weeks), this would not affect any results. The trial was funded by non-profit agencies, however, the study drugs were donated by the pharmaceutical company. One of the authors is an employee of the GSK group of companies and has restricted shares in the GSK group of companies.
Outcomes: Clinical malaria, Hospital admission, death, malaria anemia	**Overall risk:** Low risk	

[3]MVPE surveillance data

3. P Milligan and K Moore, Statistical report on the results of the RTS,S/AS01 Malaria Vaccine Pilot Evaluation 24 months after the vaccine was introduced. V1.3 Aug 2021.

ROB Domain	Judgement	Text supporting judgement
1. Was the allocation sequence adequately generated?	Low risk	"To ensure the implementation and comparison areas were similar in all ways relevant to the evaluation, except the use of the vaccine, the following key factors, which may be associated with the endpoints being evaluated, were balanced in implementation and comparison areas: malaria transmission; vaccination coverage; number of hospitals and other health facilities; geographic location; population size in clusters. The approach used is technically referred to as a balanced (or constrained) randomization". "Each country team was requested to provide the data for the randomization. In parallel, the WHO HQ statistician developed a computer program, written in R, to generate the balanced options for each country. Once data was provided, the WHO statistician ran the code to identify the balanced options for each country." Country process: "The computer programme was developed to provide a long list of acceptable permutations of the ways the clusters could be assigned, with each option assigned a unique, sequential number. Once the list of options was produced for each country, a linkage analysis was performed (reports attached as annex 3) to check that an adequate set of balanced options was accurate. This included checking that balance criteria were not overly constraining and, for example, forcing that some clusters were always - or never - allocated together. Once this was confirmed the list of balanced options was provided to the country so that one option could be selected. In each country, pieces of paper, each with the number of one of the allocation options, were folded and placed in a container. One of the pieces of paper was pulled out of the container by the designated individual at the country's randomisation event." In-depth individual country reports of the randomisation outputs are provided in the protocol.
2. Was allocation adequately concealed?	Low risk	Randomisation process was done by (an external) WHO HQ statistician who developed a computer program to generate the balanced options for each country.

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ROB Domain	Judgement	Text supporting judgement
		"The computer programme was developed to provide a long list of acceptable permutations of the ways the clusters could be assigned, with each option assigned a unique, sequential number".
3. For cluster RCTs, was there bias arising from the timing of identification and recruitment of participants? (see Figure 1)	Low risk	Clusters (i.e. areas) appear to have been randomised before recruitment of participants. The total number of clusters required for the MVIP was determined by the need for statistical power to assess the vaccine's impact on mortality.
4. Was knowledge of allocated intervention adequately prevented during study? (i.e., blinding of participants and personnel)	Unclear risk	Open label study with cluster randomised areas. However, from the household survey (HHS) findings there is no evidence that the introduction of RTS,S/AS01 had a negative effect on uptake of other childhood vaccines, ITN use, care-seeking behavior, or health worker behavior in testing and treating for febrile illness.
5. Was knowledge of allocated intervention adequately prevented during the study from outcome assessors?	Low risk	Primary outcomes of interest (impact and safety) confirmed by laboratory testing, unlikely that assessors were aware of vaccination status. "Surveillance for severe malaria and other conditions is being maintained through sentinel hospitals where diagnostic procedures have been strengthened, and surveillance for mortality has been established in the community throughout the implementation and comparison areas." According to the protocol, "for all cases with a diagnosis of meningitis, and a sample of non-meningitis diagnoses, an independent expert review, blinded to vaccine status, may be conducted on the patient's record". In the end, the assessment based on patient's record was not done as it was deemed to be unhelpful.
6. Were incomplete outcome data adequately addressed?	Low risk	Full results not available, this analysis based on power sufficient to test the safety signals identified in Phase 3 trial. No information about withdrawals and exclusions from analysis. Quote: "there were no withdrawals as we were not following patients longitudinally, however there were missing outcome data (e.g. if a lumbar puncture was not done we have missing data on their meningitis status). We noted no differences in missingness between vaccinating and comparison areas after adjustment using the age-ineligible group, so the statistical method used to calculate the rate ratios (using the age-ineligible group for adjustment) should have adequately addressed the problem of missing data if we assume that the data were missing at random."

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ROB Domain	Judgement	Text supporting judgement
7. Are reports of the study free of suggestion of selective reporting?	Low risk	Trial registry and study protocols checked, all primary outcomes at this time point (24 months) analysed and reported.
8. Was the study apparently free of other problems that could put it at high risk of bias?	Low risk	This study was funded by WHO. Regarding the statistical analysis, the MVIP statistical team, contracted from London School of Hygiene and Tropical Medicine (LSHTM), developed a statistical analysis plan for the analysis of merged data from the MVPE. The MVIP data manager maintained a database for collecting and merging data from the evaluation partners and reporting to stakeholders. Since the start of surveillance (2019), safety and impact data are received and reviewed on a monthly basis by the data manager, statisticians, WHO, and the MVPE consortium in each country.
Outcomes: Safety (cerebral malaria, severe malaria, meningitis, mortality), impact (hospitalization)	**Overall risk:** Unclear risk	No details on role of the funder within the project. Open-label study. Limited information on missing data due to study not yet being published.

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Figure 1. Suggested algorithm for reaching risk of bias judgements for bias arising from the randomization process in a cluster-randomized trial