4.3. Vaccine

Clinical Question/ PICO

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

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

Comparator: Malaria interventions currently in place without malaria vaccination

Summary

Systematic review summary Three studies form the basis of these recommendations:

two were individual randomized controlled trials (RCTs) and one was an open-label extension study of an included RCT. One was a multicentre study comparing three or four doses of the RTS,S/AS01 malaria vaccine to no malaria vaccination. The other RCT compared the RTS,S/AS01 malaria vaccine alone to SMC alone, and also compared a combination of malaria vaccine and SMC to the malaria vaccine alone or SMC alone. Based on WHO regions, all three studies were conducted in Africa, specifically: Burkina Faso (three studies), Gabon, Ghana, Kenya (two studies), Malawi, Mali, Mozambique, and the United Republic of Tanzania (two studies).

In addition, data from the observational evaluation of the first 24 months of pilot implementation in Ghana, Malawi, and Kenya were considered by MPAG/SAGE and included in the evidence summary.

The RCTs showed that RTS,S/AS01 reduces clinical malaria, hospital admissions with a positive malaria test, hospitalization with severe malaria, all-cause hospital admissions, severe malaria anaemia and the need for blood transfusions. Compared to SMC, RTS,S/AS01 is non-inferior in reducing clinical malaria and severe malaria anaemia and may be superior in reducing hospitalization with severe malaria. The combination of RTS,S/AS01 and SMC is probably better than SMC alone in reducing all-cause mortality and clinical malaria, and may reduce the need for blood transfusions and all-cause hospital admissions. The pilot programme showed that delivery of RTS,S/AS01 through routine systems probably reduces hospital admissions with severe malaria.

The RCTs had too few cases to determine an association between the vaccine and meningitis but the pilot study showed that RTS,S/AS01 introduction was probably not associated with an increase in hospital admissions with meningitis. There was uncertainty whether RTS,S/AS01 was associated with an increase in cerebral malaria in the RCTs but the pilot programme showed that vaccine introduction was probably not associated with an increase in hospital admission with cerebral malaria. One RCT found that vaccination with RTS,S/AS01 may be associated with an increase in deaths in girls, but the other found no evidence that the effect of RTS,S/AS01 (alone or in combination with SMC) on mortality differed between girls and boys compared to SMC alone. The pilot programme found that the effect of the RTS,S/AS01 vaccine introduction on all-cause mortality probably did not differ between girls and boys.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Protective efficacy (%) against clinical malaria episodes; 4-doses of RTS,S/AS01 versus control [1] Ph 3 randomized trial 2009–2014 (month 0 to end of study); median of 48 months' follow-up 6 Important	36.3 (CI 95% 31.8 — 40.5) Based on data from 5,950 participants in 1 studies. [2] (Randomized controlled) Follow up: 48 months.	Difference:	**1,774 fewer per 1000** (CI 95% 1,387 fewer — 2,186 fewer)	**High**	RTS,S/AS01 vaccination reduces clinical malaria.
Protective efficacy (%) against clinical malaria of vaccine alone versus SMC alone [3] Phase 3b randomized study 2017–2020; 3 years' follow-up	7.9 (CI 99% -1 — 16) Based on data from 3,953 participants in 1 studies. [4] (Randomized controlled)	305 per 1000 Difference:	278 per 1000 **27 fewer per 1000** (CI 95% 13 fewer — 40 fewer)	**High**	RTS,S/AS01 vaccination is non inferior to SMC in reducing clinical malaria.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important **Protective efficacy (%) against clinical malaria of vaccine + SMC combination versus SMC alone** [5] Phase 3b randomized study 2017–2020; 3 years' follow-up	62.8 (CI 95% 58.4 — 66.8) Based on data from 3,932 participants in 1 studies. [6] (Randomized controlled)	**305** per 1000 Difference:	**113** per 1000 **192 fewer per 1000** (CI 95% 182 fewer — 200 fewer)	**High**	The combination of RTS,S/AS01 vaccination with SMC is superior to SMC alone in reducing clinical malaria.
6 Important **Protective efficacy (%) against severe malaria episodes; 4 vaccine doses versus control** [7] Ph 3 randomized trial 2009–2014 (month 0 to end of study); median of 48 months' follow-up	32.2 (CI 95% 13.7 — 46.9) Based on data from 5,950 participants in 1 studies. [8] (Randomized controlled) Follow up: 48 months.	Difference:	**19 fewer per 1000** (CI 95% 4 fewer — 35 fewer)	**High** [9]	RTS,S/AS01 vaccination reduces severe malaria.
9 Critical **Protective efficacy (%) against hospitalization due to severe malaria of vaccine alone versus SMC alone** [10] Phase 3b randomized study 2017–2020; 3 years' follow-up	-0.4 (CI 95% -60.2 — 37.1) Based on data from 3,953 participants in 1 studies. [11] (Randomized controlled)	**6.8** per 1000 Difference:	**6.7** per 1000 **0.1 fewer per 1000** (CI 95% 2 fewer — 2.4 more)	**Low** Due to very serious imprecision [12]	There may be little or no difference between RTS,S/AS01 vaccination and SMC in reducing hospitalization with severe malaria.
9 Critical **Protective efficacy (%) against hospitalization**	70.5 (CI 95% 41.9 — 85) Based on data from 3,932 participants in 1	**6.8** per 1000	**2** per 1000	**Moderate** Due to serious imprecision [15]	The combination of RTS,S/AS01 vaccination with SMC may be superior to SMC alone in

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
due to severe malaria of vaccine + SMC combination versus SMC alone [13] Phase 3b randomized study 2017–2020, 3 years' follow-up 9 Critical	studies. [14] (Randomized controlled)	Difference:	**4.8 fewer per 1000** (CI 95% 3.2 fewer — 5.7 fewer)		reducing hospitalization with severe malaria.
Incidence rate ratio for impact of routine RTS,S/AS01 vaccination on hospitalization with severe malaria in implementing versus comparison areas [16] Pilot implementation study 2019–2021 (month 0 to month 24) 9 Critical	0.7 (CI 95% 0.54 — 0.92) Based on data from 27,678 participants in 1 studies. [17]			**Moderate** Due to serious imprecision [18]	RTS,S/AS01 vaccine introduction is probably associated with a reduction in incidence of hospital admissions with severe malaria.
Protective efficacy (%) against severe malaria anaemia; 4 vaccine doses versus control [19] Ph 3 randomized trial 2009–2014 (month 0 to end of study); median of 48 months' follow-up 6 Important	47.8 (CI 95% 11.6 — 69.9) Based on data from 5,950 participants in 1 studies. [20] (Randomized controlled) Follow up: 48 months.	Difference:	**11 fewer per 1000** (CI 95% 1 fewer — 24 fewer)	**Moderate** Due to serious imprecision [21]	RTS,S/AS01 vaccination probably reduces severe malaria anaemia.
Protective efficacy (%) against severe malaria anaemia of vaccine alone versus SMC alone [22] Phase 3b	18.4 (CI 95% -39.3 — 52.2) Based on data from 3,953 participants in 1 studies. [23] (Randomized controlled)	5.69 per 1000 Difference:	4.52 per 1000 **1.17 fewer per 1000** (CI 95% 2.64 fewer — 0.99 more)	**Low** Due to very serious imprecision [24]	There may be little or no difference between RTS,S/AS01 vaccination and SMC in reducing severe malaria anaemia.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
randomized study 2017–2020, 3 years' follow-up 6 Important					
Protective efficacy (%) against severe malaria anaemia of vaccine + SMC combination versus SMC alone [25] Phase 3b randomized study 2017–2020, 3 years' follow-up 6 Important	67.9 (CI 95% 34.1 — 84.3) Based on data from 3,932 participants in 1 studies. [26] (Randomized controlled)	5.69 per 1000 Difference:	1.82 per 1000 **3.87 fewer per 1000** (CI 95% 2.32 fewer — 4.71 fewer)	**Moderate** Due to serious imprecision [27]	The combination of RTS,S/AS01 vaccination with SMC may be superior to SMC alone in reducing severe malaria anaemia.
Protective efficacy (%) against blood transfusions; 4 vaccine doses versus control [28] Ph 3 randomized trial 2009–2014 (month 0 to end of study); median of 48 months' follow-up 6 Important	28.5 (CI 95% 3.5 — 47.2) Based on data from 5,950 participants in 1 studies. [29] (Randomized controlled)	Difference:	**15 fewer per 1000** (CI 95% 1 fewer — 31 fewer)	**Moderate** Due to serious imprecision [30]	RTS,S/AS01 vaccination probably reduces the need for blood transfusions.
Protective efficacy (%) against blood transfusion of vaccine alone versus SMC alone [31] Phase 3b randomized study 2017–2020; 3 years' follow-up 9 Critical	8.27 (CI 95% -67.6 — 49.8) Based on data from 3,953 participants in 1 studies. [32] (Randomized controlled)	4.22 per 1000 Difference:	3.79 per 1000 **0.43 fewer per 1000** (CI 95% 1.75 fewer — 1.6 more)	**Low** Due to very serious imprecision [33]	There may be little or no difference between RTS,S/AS01 vaccination and SMC in reducing the need for blood transfusions.
Protective efficacy (%) against blood	65.4 (CI 95% 22.9 — 84.5) Based on data from	4.22 per 1000	1.45 per 1000	**Low** Due to very serious	The combination of RTS,S/AS01 vaccination with SMC may be

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
transfusions of vaccine + SMC combination versus SMC alone [34] Phase 3b randomized study 2017–2020; 3 years' follow-up 9 Critical	3,932 participants in 1 studies. [35] (Randomized controlled)	Difference:	**2.77 fewer per 1000** (CI 95% 1.32 fewer — 3.49 fewer)	imprecision [36]	superior to SMC alone in reducing the need for blood transfusions.
Protective efficacy (%) against all-cause hospital admissions; 4 vaccine doses versus control [37] Ph 3 randomized trial 2009–2014 (month 0 to end of study); median of 48 months' follow-up 9 Critical	16.5 (CI 95% 7.2 — 24.9) Based on data from 5,950 participants in 1 studies. [38] (Randomized controlled)	Difference:	**59 fewer per 1000** (CI 95% 18 fewer — 103 fewer)	**High** [39]	RTS,S/AS01 vaccination reduces all-cause hospital admissions.
Protective efficacy (%) against all-cause hospital admissions of vaccine alone versus SMC alone [40] Phase 3b randomized study 2017–2020; 3 years' follow-up 9 Critical	-22.3 (CI 95% -74.4 — 14.3) Based on data from 3,953 participants in 1 studies. [41] (Randomized controlled)	**11** per 1000 Difference:	**13.2** per 1000 **2.2 more per 1000** (CI 95% 0.5 fewer — 5.6 more)	**Low** Due to very serious imprecision [42]	There may be little or no difference between RTS,S/AS01 vaccination and SMC in reducing all-cause hospital admissions.
Protective efficacy (%) against all-cause hospital admissions of vaccine + SMC combination versus SMC alone [43] Phase 3b randomized study 2017–2020; 3 years' follow-up	18.7 (CI 95% -19.4 — 44.7) Based on data from 3,932 participants in 1 studies. [44] (Randomized controlled)	**11** per 1000 Difference:	**8.9** per 1000 **2.1 fewer per 1000** (CI 95% 4.28 fewer — 0.8 more)	**Low** Due to very serious imprecision [45]	The combination of RTS,S/AS01 vaccination with SMC may be superior to SMC alone in reducing all-cause hospital admissions.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical **Incidence rate ratio for impact of routine RTS,S/AS01 vaccination on all-cause hospital admissions in implementing versus comparison areas** [46] Pilot implementation study 2019–2021 (month 0 to month 24)	0.92 (CI 95% 0.83 — 1.03) Based on data from 27,678 participants in 1 studies. [47]			**Moderate** Due to serious imprecision [48]	RTS,S/AS01 vaccine introduction probably has little or no difference on all-cause hospital admissions.
9 Critical **Incidence rate ratio for impact of routine RTS,S/AS01 vaccination on hospital admissions with a positive malaria test in implementing versus comparison areas** [49] Pilot implementation study 2019–2021 (month 0 to month 24)	0.79 (CI 95% 0.68 — 0.93) Based on data from 27,678 participants in 1 studies. [50]			**High** [51]	RTS,S/AS01 vaccine introduction is associated with reduced hospital admissions with a positive malaria test.
9 Critical **Protective efficacy (%) against all-cause mortality; 3 or 4 vaccine doses versus control** [52] Ph 3 randomized trial 2009–2014 (month 0 to end of study); median of 48 months' follow-up	Based on data from 8,922 participants in 1 studies. [53] (Randomized controlled)			**Low** Due to very serious imprecision [54]	There were too few deaths to determine the impact of RTS,S/AS01 vaccination on all-cause mortality.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical **Protective efficacy (%) against all-cause mortality; vaccine alone versus SMC alone** [55] Phase 3b randomized study 2017–2020; 3 years' follow-up	12.1 (CI 95% -55.7 — 50.4) Based on data from 3,953 participants in 1 studies. [56] (Randomized controlled)	4.59 per 1000 Difference:	3.97 per 1000 **0.62 fewer per 1000** (CI 95% 1.97 fewer — 1.45 more)	**Low** Due to very serious imprecision [57]	There may be little or no difference between the impact of RTS,S/AS01 vaccination and SMC administration on all-cause mortality.
9 Critical **Protective efficacy (%) against all-cause mortality of vaccine + SMC combination versus SMC alone** [58] Phase 3b randomized study 2017–2020; 3 years' follow-up	52.3 (CI 95% 4.99 — 76) Based on data from 3,932 participants in 1 studies. [59] (Randomized controlled)	4.59 per 1000 Difference:	2.18 per 1000 **2.41 fewer per 1000** (CI 95% 0.75 fewer — 3.35 fewer)	**Moderate** Due to serious imprecision [60]	The combination of RTS,S/AS01 vaccination and SMC is probably associated with a reduction in all-cause mortality.
9 Critical **Incidence rate ratio of meningitis; 3 or 4 vaccine doses versus control** [61] Post-hoc analysis of Ph 3 randomized trial 2009–2014	10.5 (CI 95% 1.41 — 78) Based on data from 8,922 participants in 1 studies. [62]			**Low** Due to serious risk of bias, Due to serious imprecision [63]	There were too few meningitis cases to determine an association with RTS,S/AS01 vaccination.
9 Critical **Incidence rate ratio of meningitis in vaccine alone versus SMC alone versus combination of vaccine with SMC** [64] Phase 3b	Based on data from 6,861 participants in 1 studies. [65] (Randomized controlled)			**Low** Due to very serious imprecision [66]	There were no meningitis cases to determine an association with RTS,S/AS01 vaccination.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
randomized study 2017–2020; 3 years' follow-up 9 Critical					
Incidence rate ratio of hospital admissions with meningitis; vaccine implementing versus comparison areas [67] Pilot implementation study 2019–2021 (month 0 to month 24) 9 Critical	0.81 (CI 95% 0.43 — 1.55) Based on data from 27,678 participants in 1 studies. [68]			**Moderate** Due to serious imprecision [69]	There is probably no evidence that RTS,S/AS01 vaccine introduction is associated with an increase in hospital admissions with meningitis.
Incidence rate ratio of possible cerebral malaria; 4-dose + 3-dose versus control groups [70] Post-hoc analysis of Ph 3 randomized trial 2009–2014 9 Critical	2.15 (CI 95% 1.1 — 4.3) Based on data from 8,922 participants in 1 studies. [71]			**Very low** Due to very serious risk of bias and serious imprecision [72]	There is uncertainty whether RTS,S/AS01 vaccination is associated with an increase in cerebral malaria cases.
Incidence rate ratio of cerebral malaria in vaccine alone versus SMC alone vs combination of vaccine with SMC [73] Phase 3b randomized study 2017–2020; 3 years' follow-up 9 Critical	Based on data from 5,920 participants in 1 studies. [74] (Randomized controlled)			**Low** Due to very serious imprecision [75]	There were too few cerebral malaria cases to determine an association with RTS,S/AS01 vaccination.
Incidence rate ratio of hospital	0.77 (CI 95% 0.44 — 1.35)			**Moderate** Due to serious	There is probably no evidence that RTS,S/

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
admissions with cerebral malaria; vaccine implementing versus comparison areas [76] Pilot implementation study 2019–2021 (month 0 to month 24) 9 Critical	Based on data from 27,678 participants in 1 studies. [77]			inconsistency and serious imprecision [78]	AS01 vaccine introduction is associated with an increase in hospital admissions with cerebral malaria.
Female:male risk ratio of vaccine impact on all-cause mortality; 4-dose + 3-dose versus control groups [79] Post-hoc analysis of Ph 3 randomized trial 2009–2014 9 Critical	1.5 (CI 95% 1.03 — 2.08) Based on data from 8,922 participants in 1 studies. [80]			**Low** Due to very serious imprecision [81]	RTS,S/AS01 vaccination may be associated with an increase in deaths in girls and a decrease in deaths in boys.
Female:male rate ratio on vaccine impact on all-cause mortality; vaccine alone versus SMC alone [82] Phase 3b randomized study 2017–2020; 3 years' follow-up 9 Critical	1.8 (CI 95% 0.56 — 5.79) Based on data from 3,953 participants in 1 studies. [83] (Randomized controlled)			**Low** Due to very serious imprecision [84]	There may be no evidence that the effect of RTS,S/AS01 vaccination differs between girls and boys.
Female:male rate ratio for all-cause mortality; combination of vaccine with SMC versus SMC alone [85] Phase 3b randomized study 2017–2020; 3 years' follow-up	0.35 (CI 95% 0.06 — 1.98) Based on data from 3,932 participants in 1 studies. [86] (Randomized controlled)			**Low** Due to very serious imprecision [87]	There may be no evidence that the effect of RTS,S/AS01 vaccination differs between girls and boys.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical **Female:male rate ratio of all-cause mortality ratio; vaccine implementing versus comparison areas** [88] Pilot implementation study 2019–2021 (month 0 to month 24) 9 Critical	1.08 (CI 95% 0.93 — 1.25) Based on data from 13,682 participants in 1 studies. [89]			**Moderate** Due to serious imprecision because not yet powered to assess overall impact on all-cause mortality, however well powered to detect gender imbalance in all-cause mortality [90]	There is probably no evidence that the effect of RTS,S/AS01 vaccine introduction on all-cause mortality differs between girls and boys.

1. 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 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); 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; Protective efficacy = (1-hazard ratio); Per Protocol analysis: VE 28.5% (95% CI 6.3 to 45.7)
2. Primary study[89]. The number of cases averted over time was calculated as the sum of 3-monthly differences in the estimated number of cases between the control and the RTS,S/AS01 groups (R3R and R3C combined up to the time of booster dose and R3R and R3C separately after the booster dose) and expressed per 1000 participants vaccinated. Among the older children, in the 12 months following administration of the first three doses, vaccine efficacy against clinical (uncomplicated and severe) malaria was 51% (95% CI 47-55) (per protocol analysis). **Baseline/comparator:** . **Supporting references:** [89],
3. 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).
4. Primary study[91]. The RTS,S vaccine alone group had 1,540 clinical malaria cases over 5535.7 total person-years at risk (PYAR) for an incidence rate of 278 cases (95% CI: 264.6 to 292.4) per 1000 PYAR; The SMC alone group had 1,661 cases over 5449.9 total PYAR for an incidence rate of 305 cases (95% CI: 290.5 to 319.8) per 1000 PYAR;. **Baseline/comparator:** . **Supporting references:** [91], The 90, 95, and 99% CIs for the hazard ratio (HR) all excluded the pre-specified non-inferiority margin of 1.20..
5. 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).
6. Primary study[91]. The RTS,S + SMC combined group had 624 clinical malaria cases over 5508.0 total PYAR for an incidence rate of 113 cases (95% CI: 104.7 to 122.5) per 1000 PYAR; The SMC alone group has 1,661 cases over 5449.9 total PYAR for an incidence rate of 305 cases (95% CI: 290.5 to 319.8) per 1000 PYAR;. **Baseline/comparator:** . **Supporting references:** [91],

7. 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 acoexisting 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). 4-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. Protective efficacy = (1-hazard ratio). Per Protocol analysis: VE 28.5% (95%CI: 6.3 to 45.7)
8. Primary study[89]. Among the older children, in the 12 months following administration of the first three doses, vaccine efficacy against severe malaria was 45% (95% CI 22-60) (per protocol analysis).. **Baseline/comparator:** . **Supporting references:** [89], PP analysis VE: 28.5% (95% CI: 6.3 to 45.7); The number of cases averted overtime was calculated as the sum of 3-monthly differences in the estimated number of cases between the control and the RTS,S/AS01 groups (R3R and R3C combined up to the time of booster dose and R3R and R3C separately after the booster dose) and expressed per 1000 participants vaccinated..
9. **Risk of Bias: no serious.** Study was rated as unclear risk of bias due to heavy involvement of the funder in the project; however, it has not been downgraded for risk of bias as this was the only concern and the study was carefully scrutinized by independent experts and considered well conducted.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
10. 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).
11. Primary study[91]. The RTS,S vaccine alone group had 37 severe malaria cases (of which 25 were severe malaria anaemia) over 5535.7 total PYAR for an incidence rate of 6.7 severe malaria cases (95% CI: 4.8 to 9.2) per 1000 PYAR; The SMC alone group had 37 cases (of which 31 were severe malaria anaemia) over 5449.9 total PYAR for a rate of 6.8 cases (95% CI: 4.9 to 9.4) per 1000 PYAR;. **Baseline/comparator:** . **Supporting references:** [91], Most cases of severe malaria were severe malaria anaemia (vaccine: 25/37; SMC: 31/37).
12. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm. **Publication bias: no serious.**
13. 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).
14. Primary study[91]. Combination group of RTS,S + SMC had 11 severe malaria cases (of which 10 were severe malaria anaemia) over 5508 total PYAR for an incidence rate of 2.0 severe malaria cases (95% CI: 1.1 to 3.6) per 1000 PYAR; The SMC alone group has 37 cases (of which 31 were severe malaria anaemia) over 5449.9 total PYAR for a rate of 6.8 cases (95% CI: 4.9 to 9.4) per 1000 PYAR;. **Baseline/comparator:** . **Supporting references:** [91],
15. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and large CI. **Publication bias: no serious.**
16. Pilot implementation study designed to be analysed using cluster randomized control methodology. Across the three countries, there was a total of 27 678 admissions to sentinel hospitals in children 1-59 months during the period from vaccine introduction until 30 April 2021: 4,853 were vaccine-eligible based on their date of birth out of 13,918 total admissions in areas where the vaccine was provided (implementating areas); 5,141 were vaccine-eligible out of 13,760 total admissions in comparison areas
17. [101]. Among children eligible to have received all three primary doses of RTS,S/AS01, there was a total of 1107 admissions with severe malaria (out of 9,994 total age-eligible admissions), 418 from implementation areas and 689 from comparison areas. Among children who were not eligible there were 2,703 total admissions with severe malaria (out of 17,684 total age-ineligible admissions) to have received any doses of RTS,S/AS01: 1313 from implementation areas and 1390 from comparison areas. The incidence rate ratio comparing incidence of admission with severe malaria between implementing and comparison areas was 0.70 (95%CI 0.54 to 0.92), a reduction of 30% (95%CI 8% to 46%); there was no evidence that effectiveness differed between cerebral malaria and other forms of severe malaria. **Baseline/comparator:** .
18. **Risk of Bias: no serious.** Not downgraded for risk of bias despite being an open-label study because the findings from the household survey suggestthere is no evidence that the introduction of RTS,S/AS01 had a negative effect on the uptake of other childhood vaccines, ITN use, care-seeking behaviour, or health worker behaviour in testing and treating for febrile illness.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level for imprecision: few events and large CI. **Publication bias: no serious.**
19. 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.

4-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. Protective efficacy = (1-hazard ratio).
20. Primary study[89]. **Baseline/comparator:** .
21. **Risk of Bias: no serious.** 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 was carefully scrutinized by independent experts and considered well conducted.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and large confidence interval. **Publication bias: no serious.**
22. 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).
23. Primary study[91]. The RTS,S vaccine group had 25 severe malaria anemia cases over 5535.7 total PYAR for an incidence rate of 4.52 cases (95% CI: 3.05 to 6.68) per 1000 PYAR; The SMC alone group has 31 cases over 5449.9 total PYAR for a rate of 5.69 cases (95% CI: 4.00 to 8.09) per 1000 PYAR;. **Baseline/comparator:** . **Supporting references:** [91],
24. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large confidence interval that incorporates the possibility of benefit and harm. **Publication bias: no serious.**
25. 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).
26. Primary study[91]. The RTS,S vaccine and SMC combination group had 10 severe malaria anaemia cases over 5508 total PYAR for an incidence rate of 1.82 cases (95% CI: 0.977 to 3.37) per 1000 PYAR; The SMC alone group had 31 cases over 5449.9 total PYAR for a rate of 5.69 cases (95% CI: 4.00 to 8.09) per 1000 PYAR;. **Baseline/comparator:** . **Supporting references:** [91],
27. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and a very large CI. **Publication bias: no serious.**
28. 4-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. Protective efficacy = (1-hazard ratio).
29. Primary study[89]. **Baseline/comparator:** .
30. **Risk of Bias: no serious.** Study was rated as unclear risk of bias due to heavy involvement of the funder in the project; however, it has not been downgraded for risk of bias as this was the only concern and the study was carefully scrutinized by independent experts and considered well conducted.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and large CI. **Publication bias: no serious.**
31. 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).
32. Primary study[91]. The RTS,S vaccine group had 21 blood transfusion events over 5535.7 total PYAR for an incidence rate of 3.79 events (95% CI: 2.47 to 5.82) per 1000 PYAR; The SMC alone group had 23 events over 5449.9 total PYAR for an incidence rate of 4.22 events (95% CI: 2.80 to 6.35) per 1000 PYAR;. **Baseline/comparator:** . **Supporting references:** [91],
33. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm. **Publication bias: no serious.**
34. 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).
35. Primary study[91]. The RTS,S vaccine and SMC combination group had 8 blood transfusion events over 5508.0 total PYAR for an incidence rate of 1.45 events (95% CI: 0.726 to 2.90) per 1000 PYAR; The SMC alone group has 23 events over 5449.9 total PYAR for an incidence rate of 4.22 events (95% CI: 2.80 to 6.35) per 1000 PYAR;. **Baseline/comparator:** . **Supporting references:** [91],
36. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm. **Publication bias: no serious.**
37. 4-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. Protective efficacy = (1-hazard ratio).
38. Primary study[89]. **Baseline/comparator:** .
39. **Risk of Bias: no serious.** Study was rated as unclear risk of bias due to heavy involvement of the funder in the project; however, it has not been downgraded for risk of bias as this was the only concern and the study was carefully scrutinized by independent experts and considered well conducted.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no**

serious. Publication bias: no serious.
40. 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).
41. Primary study[91]. The RTS,S vaccine group had 73 events over 5535.7 total PYAR for an incidence rate of 13.2 events (95% CI: 10.5 to 16.6) per 1000 PYAR; The SMC alone group had 60 events over 5449.9 total PYAR for an incidence rate of 11.0 events (95% CI: 8.55 to 14.2) per 1000 PYAR;. **Baseline/comparator:** .
42. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm. **Publication bias: no serious.**
43. 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).
44. Primary study[91]. The RTS,S vaccine and SMC combination group had 49 events over 5508 total PYAR for an incidence rate of 8.90 events (95% 6.72 to 11.8) per 1000 PYAR; The SMC alone group had 60 events over 5449.9 total PYAR for an incidence rate of 11.0 events (95% CI: 8.55 to 14.2) per 1000 PYAR;. **Baseline/comparator:** . **Supporting references:** [91],
45. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm. **Publication bias: no serious.**
46. Pilot implementation study designed to be analysed using cluster randomized control methodology. Across the three countries, there was a total of 27,678 admissions to sentinel hospitals in children 1-59 months during the period from vaccine introduction until 30 April 2021: 4,853 were vaccine-eligible based on their date of birth out of 13,918 total admissions in areas where the vaccine was provided (implementating areas); 5,141 were vaccine-eligible out of 13,760 total admissions in comparison areas
47. [101]. Severe malaria represented 19% of all admissions to sentinel hospitals (with at least one overnight stay) in comparison areas among children who were eligible to receive three doses of malaria vaccine. In this age group, there was a total of 3196 admissions to sentinel hospitals in implementation areas and 3569 in comparison areas. 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%).. **Baseline/comparator:** .
48. **Risk of Bias: no serious.** 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 behaviour, or health worker behaviour in testing and treating for febrile illness.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: large CI 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.. **Publication bias: no serious.**
49. Pilot implementation study designed to be analysed using cluster randomized control methodology. Across the three countries, there were a total of 27,678 admissions to sentinel hospitals in children 1-59 months during the period from vaccine introduction until 30 April 2021: 4,853 were vaccine-eligible based on their date of birth out of 13,918 total admissions in areas where the vaccine was provided (implementing areas); 5,141 were vaccine-eligible out of 13,760 total admissions in comparison areas.
50. [101]. Patients admitted to sentinel hospitals were routinely tested for malaria infection by rapid diagnostic test (RDT) or microscopy. Out of a total of 27,678 patients admitted, test results were available for 88%. Among children eligible to have received three vaccine doses, the number of patients admitted with a positive malaria test was 2630-- 1075 from implementation areas and 1555 from comparison areas. 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%).. **Baseline/comparator:** .
51. **Risk of Bias: no serious.** 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 behaviour, or health worker behaviour in testing and treating for febrile illness.; . **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
52. 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. Protective efficacy = (1-hazard ratio).
53. [89]. Four dose group: 61 deaths (13 malaria)/2976 children + Three dose group: 51 deaths (17 malaria) / 2972 children vs Control group: 46 deaths (13 malaria) / 2974 children.. **Baseline/comparator:** .
54. **Risk of Bias: no serious.** Study was rated as unclear risk of bias due to heavy involvement of the funder in the project;

however, it has not been downgraded for risk of bias as this was the only concern and the study was carefully scrutinized by independent experts and considered well conducted. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm; . **Publication bias: no serious.**

55. 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).

56. Primary study[91]. In the RTS,S vaccine alone group there were 22 deaths total/1734 participants or 3.97 deaths (95% CI 2.92 to 6.04) per 1000 PYAR. In the SMC alone group, there were 25 deaths total/1716 participants or 4.59 deaths (95% CI 3.10 to 6.79) per 1000 PYAR.. **Baseline/comparator:** .

57. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large confidence interval that incorporates the possibility of benefit and harm; . **Publication bias: no serious.**

58. 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).

59. Primary study[91]. In the RTS,S vaccine + SMC combination group there were 12 deaths total/1740 children or 2.18 deaths (95% CI 1.24 to 3.84) per 1000 PYAR. In the SMC alone group, there were 25 deaths total/1716 children or 4.59 deaths (95% CI 3.10 to 6.79) per 1000 PYAR.. **Baseline/comparator:** .

60. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and large CI.. **Publication bias: no serious.**

61. mITT analysis; 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. Protective efficacy = (1-hazard ratio).

62. [89]. 4-dose group 11/2976 + 3-dose group 10/2972 vs Control group 1/2974. **Baseline/comparator:** .

63. **Risk of Bias: serious.** This outcome was not pre-specified in the protocol (post-hoc analysis). Study was rated as unclear risk of bias due to heavy involvement of the funder within the project.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and large confidence interval; . **Publication bias: no serious.**

64. 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).

65. Primary study[91]. Eight cases of clinically suspected meningitis (four in the SMC-alone group, three in the RTS,S vaccine-alone group, and one in the RTS,S + SMC combined group) were investigated with the use of lumbar puncture, but none showed proven meningitis.. **Baseline/comparator:** .

66. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels for imprecision: no events reported in any groups. **Publication bias: no serious.**

67. Pilot implementation study designed to be analysed using cluster randomized control methodology; 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. Across the three countries, there was a total of 27,678 admissions to sentinel hospitals in children 1-59 months during the period from vaccine introduction until 30 April 2021: 4,853 were vaccine-eligible based on their date of birth out of 13,918 total admissions in areas where the vaccine was provided (implementing areas); 5,141 were vaccine-eligible out of 13,760 total admissions in comparison areas

68. Primary study[101]. A total of 4,311 suspected cases of meningitis were investigated. Lumbar punctures were performed in 2,652 (62%) of these patients, and PCR analysis of samples of cerebrospinal fluid (CSF) was available for 2,249 patients (52%). A total of 51 cases of probable or confirmed meningitis were seen in sentinel hospitals among age groups of children eligible for the malaria vaccine: 27 from implementation areas and 24 from comparison areas. Among the age groups that were not eligible for the malaria vaccine, there were 79 probable or confirmed cases of meningitis: 44 from implementation areas and 35 from comparison areas. The incidence rate ratio comparing rates of admission with meningitis in implementation and comparison areas, among vaccine-eligible children, was 0.81 (95%CI 0.43 to 1.55). There was therefore no evidence that introduction of the malaria vaccine led to an increase in the incidence of hospital admission with meningitis. There were sufficient cases and high coverage of the vaccine to detect an excess of the magnitude observed in the Phase 3 trial if it had occurred. Of the patients with probable or confirmed meningitis in vaccine-eligible age groups from implementation areas, 41% (11/27) had received the RTS,S/AS01 vaccine, compared to 53% (2491/4672) of all other hospital admissions in this age group from implementation areas (odds ratio, adjusted for country and age: 0.73 (95%CI 0.31,1.71). The PCR results showed that only 15% (8/55) of samples from confirmed cases, were of vaccine serotypes preventable by Hib or pneumococcus vaccines (i.e. Haemophilus influenzae type b, or vaccine serotypes of Streptococcus

pneumoniae).. **Baseline/comparator:** .
69. **Risk of Bias: no serious.** 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 behaviour, or health worker behaviour in testing and treating for febrile illness. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: large CI 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 (RR = 4.5-10.5), after allowing for vaccine uptake levels in the pilot.. **Publication bias: no serious.**
70. 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).
71. [89]. In the context of an overall decrease in severe malaria, in an unplanned subgroup analysis from study months 0 to 20, 13 cases of possible cerebral malaria by record review and expert opinion occurred in the combined 3- and 4-dose RTS,S/AS01 group compared to 7 in the control group (2:1 randomization). From study month 21 until trial end, there were 7 cerebral malaria cases in the 4-dose RTS,S/AS01 group, 8 cases in the 3-dose RTS,S/AS01 group, and 2 cases in the control group. **Baseline/comparator:** .
72. **Risk of Bias: very serious.** Downgraded two levels for risk of bias: 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 more difficult through record review Study was rated as unclear risk of bias due to heavy involvement of the funder in the project; however, it has not been downgraded for risk of bias for this reason. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and large CI. **Publication bias: no serious.**
73. 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).
74. Primary study[91]. 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).. **Baseline/comparator:** .
75. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: very few events and 0 events in the control arm; . **Publication bias: no serious.**
76. Pilot implementation study designed to be analysed using cluster randomized control methodology; 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. Across the three countries, there was a total of 27,678 admissions to sentinel hospitals in children 1-59 months during the period from vaccine introduction until 30 April 2021: 4,853 were vaccine-eligible based on their date of birth out of 13,918 total admissions in areas where the vaccine was provided (implementing areas); 5,141 were vaccine-eligible out of 13,760 total admissions in comparison areas
77. [101]. There were 55 cases of cerebral malaria, in whom lumbar puncture was performed to exclude cases with probable meningitis): 25 from implementation areas and 30 from comparison areas. Among age groups of children not eligible to receive the malaria vaccine, there were 241 cases of cerebral malaria, 115 from implementation areas and 126 from comparison areas. The incidence rate ratio comparing rates of admission to hospital with cerebral malaria in implementation areas relative to comparison areas, among children eligible for the malaria vaccine, was 0.77 (95%CI 0.44 to 1.35). The incidence rate ratio for admission with other forms of severe malaria excluding cerebral malaria was 0.70 (95%CI 0.54 to 0.89). There was no evidence that effectiveness differed between cerebral malaria and other forms of severe malaria (relative rate ratio 0.94 (95%CI 0.57 to 1.56; and test of interaction p-value: 0.808). When the analysis was broadened to include cases meeting the criteria for cerebral malaria but in whom lumbar puncture was not performed, there was a total of 103 cases in age-groups eligible to have received at least one dose of the malaria vaccine: 49 from implementation areas and 54 from comparison areas. There were 455 cases in non-eligible age groups: 230 from implementing areas and 225 from comparison areas. The incidence rate ratio comparing rates of admission to hospital with cerebral malaria (with the broader case definition) in implementation areas relative to comparison areas, among children eligible for the malaria vaccine, was 0.96 (95%CI 0.61 to 1.52). Again there was no evidence that impact differed between cerebral malaria and other forms of severe malaria (test of interaction p-value: 0.470). Similar results were obtained when cerebral malaria was limited to cases defined as U (unresponsive) on the AVPU score. Among children eligible tohave received the vaccine, 20 of the cases from implementation areas and 25 from comparison areas met this stricter criterion, and the estimate of the rate ratio was 0.66 (95%CI: 0.31 to 1.43). Of the patients with cerebral malaria in vaccine-eligible age groups from implementation areas, 47% (23/49) had received RTS,S/AS01 vaccine, compared to 53% (2479/4650) of all other admissions in this age group from

implementation areas (odds ratio, adjusted for country and age,1.03, 95%CI 0.56,1.90; the odds ratio among cases meeting the stricter definition requiring a lumbar puncture was 1.58; 95%CI: 0.66 to 3.80). There was therefore no evidence that introduction of the malaria vaccine led to an increase in the incidence of hospital admission with cerebral malaria. The incidence rate ratio 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. **Baseline/comparator:** .

78. **Risk of Bias: no serious.** 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 behaviour, or health worker behaviour in testing and treating for febrile illness.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: large CI that incorporates the possibility of benefit and harm. Study was powered for a pooled analysis only; country estimates vary but CIs are wide and consistent with pooled effect; .

79. All-cause mortality (month 0 to study end) (modified ITT analysis); 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.

80. [89]. Incidence rate ratio (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. **Baseline/comparator:** .

81. **Risk of Bias: no serious.** Study was rated as unclear risk of bias due to heavy involvement of the funder in the project; however, it has not been downgraded for risk of bias as this was the only concern and the study was carefully scrutinized by independent experts and considered well conducted.. **Inconsistency: no serious. Indirectness: no serious.** 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. **Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm; . **Publication bias: no serious.**

82. 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).

83. Primary study[91]. Gender interaction parameter 1.80 (95%CI: 0.56 to 5.79); Girls only RTS,S vs SMC alone hazard ratio (HR) 1.23 (95% CI: 0.51 to 2.96); there were 11 deaths total or 4.15 deaths per 1000 PYAR (95% CI 2.30 to 7.49) among girls in the RTS,S alone group compared to 9 deaths total or 3.42 deaths per 1000 PYAR (95% CI 1.78 to 6.57) among girls in the SMC alone group. Boys only RTS,S vs SMC alone HR 0.68 (95% CI 0.32 to 1.47); there were 11 deaths total or 3.82 deaths per 1000 PYAR (95% CI 2.11 to 6.89) among boys in the RTS,S alone group compared to 16 deaths total or 5.68 deaths per 1000 PYAR (95% CI 3.48 to 9.27) among boys in the SMC alone group. **Baseline/comparator:** .

84. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm; . **Publication bias: no serious.**

85. 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).

86. Primary study[91]. Gender interaction parameter 0.35 (95%CI 0.06 to 1.98). Girls only RTS,S+SMC combination group vs SMC alone group hazard ratio (HR) 0.22 (95% CI 0.05 to 1.02); there were 2 deaths total or 0.75 deaths per 1000 PYAR (95% CI 0.19 - 3.01) among girls in the RTS,S + SMC combination group compared to 9 deaths total or 3.42 deaths per 1000 PYAR (95% CI 1.78 - 6.57) among girls in the SMC alone group. Boys only RTS,S + SMC combination group vs SMC alone group HR 0.62 (95% CI 0.28 to 1.37); there were 10 deaths total or 3.51 deaths per 1000 PYAR (95% CI 1.89 - 6.52) among boys in the Combination group compared to 16 deaths total or 5.68 deaths per 1000 PYAR (95% CI 3.48 - 9.27) among boys in the SMC alone group.. **Baseline/comparator:** .

87. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm;. **Publication bias: no serious.**

88. Pilot implementation study designed to be analysed using cluster randomized control methodology. The evaluation was not powered at this time point to assess the overall impact of vaccine introduction on mortality but 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. 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).

89. [101]. 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. Excluding deaths due to injury in children eligible to have received three doses of RTS,S/AS01, there was a total of 2864 deaths reported, 1421 from implementing regions and 1443 from comparison regions. In children who were not eligible to have received the vaccine there were 4218 deaths in implementing regions and 3874 in comparison regions. 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; the relative mortality ratio (girls:boys) was 1.08 (95%CI: 0.92 to 1.28). When analysis was extended to children eligible to have received at least one dose of the vaccine, similar results were obtained (ratio of mortality ratios: 1.08; 95%CI: 0.93 to 1.25; p-value for the interaction: 0.321). Similar results were also obtained when the analysis was repeated for different age groups of eligible children (mortality ratio girls:boys in eligible children under 18 months of age was 1.10 [95%CI: 0.94 to 1.29], and in eligible children aged 18 months and over it was 0.95 [95%CI: 0.70 to 1.31]). The vaccination status of vaccine-eligible children who died in implementation areas was similar in girls and boys (58.9% and 57.0% respectively). According to the household surveys in 12-23 month olds, coverage of the first dose of RTS,S/AS01 was slightly higher in girls than in boys (77.6% in girls and 73.0% in boys in Ghana; 75.1% in girls and 70.1% in boys in Malawi; and 79.0% in girls and 78.2% in boys in Kenya). Coverage was similar for the third dose.. **Baseline/comparator:** .

90. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** 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.. **Publication bias: no serious.**

References

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