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