SAGE/MPAC evidence to recommendations table on the use of malaria vaccines[i,ii,iii]

Question: Should 4 doses of RTS,S/AS01 be introduced into national immunization programs of countries in Sub-Saharan Africa with medium-high malaria parasite transmission?

Population: Children ≥5 months in Sub-Saharan Africa
Intervention: 4 doses of RTS,S/AS01 (given as a 3-dose initial series with a minimum interval between doses of 4 weeks, followed by a 4th dose at 15–18 months following the 3rd dose to children as close as possible to the age of 5 months) in context of implemented other malaria prevention methods (e.g. long-lasting insecticide-treated nets), rapid diagnosis and effective treatment.
Comparison(s): No vaccination in context of implemented other malaria preventive methods (e.g. long-lasting insecticide-treated nets), rapid diagnosis and effective treatment.
Outcome: Occurrence of severe malaria caused by *P. falciparum.*

Background:
In most African countries substantial malaria-control efforts have been implemented, including the widespread deployment of long-lasting insecticide-treated bed-nets, the use of indoor residual spraying of insecticide in some settings, prompt diagnosis using quality assured rapid diagnostic tests and by using highly effective artemisinin-combination therapies. Malaria is preventable and mortality rates have fallen by 60% globally since 2000. Nevertheless, an estimated 438 000 deaths occurred due to malaria in 2015 mainly in children younger than 5 years, with over 90% of these deaths reported from sub-Saharan Africa, and nearly all of the remaining occurring in South-East Asia, the Indian subcontinent and South America.

There is one malaria vaccine candidate that has completed pivotal phase 3 evaluation. This candidate received a positive regulatory assessment by the European Medicines Agency (EMA) in 2015.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
		No	*Uncertain*	*Yes*	*Varies by setting*		
PROBLEM	Is the problem a public health priority?	☐	☐	☒	☐	According to the latest WHO estimates, there were 438 000 deaths in 2015, with over 90% of these deaths occurring in sub-Saharan Africa, and nearly all of the remaining occurring in South-East Asia, the Indian subcontinent and South America. Most deaths occur in children under 5 years of age. The	Malaria may be a threat to travelers to endemic countries, but given the available preventive measures and treatment possibilities, this group is not targeted by the recommendations developed by SAGE/MPAC.

			burden of morbidity is high with estimated 214 million new cases of malaria worldwide in 2015.	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the anticipated desirable effects substantial?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	Among trial participants given a 4-dose schedule at 5-17 months of age, vaccine efficacy against severe malaria up to the end of the trial was 31.5% (95%CI 9.3, 48.3). Given the low mortality rate within the study settings, data deriving from the trials were insufficient to draw conclusions on the outcome of mortality therefore severe malaria is the outcome assessed, as a proxy for mortality.	When given at 5-17 months of age, vaccine efficacy against all episodes of severe malaria in the first 12 months after the third dose was 44.5% (95%CI 23.8, 59.6). Up to 18 months, the efficacy was estimated at 37.7% (95%CI 18.0, 52.6). In the group receiving a 3-dose schedule, the overall efficacy was estimated at -2.2% (95%CI -31.3, 20.4) by the end of the trial. This suggests that three doses alone had no effect on the overall incidence of severe malaria, the protective effect in the first 18 months being balanced by an increase in cases in the period from 18 months to the end of the trial. Vaccine efficacy against severe malaria was lower when immunization was initiated at an age of 6-12 weeks.

	Harms of the intervention Are anticipated undesirable effects acceptable?	*No* ☐ *Uncertain* ☒ *Yes* ☐ *Varies* ☐	There was one identified risk (febrile seizures) for RTS,S/AS01 and three safety signals (meningitis, cerebral malaria and all-cause mortality in girls) that emerged from the Phase 3 trial and that will require further exploration in post-licensure studies. Further, there may be deleterious effects on the use of other preventive measures should it not be clearly communicated to the caregivers of the target population that the vaccine only provides low to moderate efficacy and this only after receipt of four doses.	Definition of safety signal (Practical aspects of signal detection in pharmacovigilance. CIOMS Working Group VIII, Geneva, CIOMS 2010): Information that arises from one or multiple sources (including observations and experiments) which suggest a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.
	Balance between benefits and harms	*Favours intervention* ☐ *Favours comparison* ☐ *Favours both* ☐ *Favours neither* ☐ *Unclear* ☒	There are benefits of the vaccine to protect against clinical and severe malaria, as well as all-cause hospitalization due to malaria. The benefits against malaria-related mortality and all-cause mortality are unknown. There is an identified risk of febrile convulsions following vaccination. A significant risk difference was observed for meningitis following vaccination, yet the causal relationship remains to be assessed. It is uncertain whether the imbalance of cerebral malaria cases	

			seen in the trial is actually due to the vaccine. The benefits are assumed to outweigh the risks for a 4-dose schedule. However, there is concern that attaining high coverage of 4-dose schedule is not feasible, and the risk profile of the vaccine requires further evaluation to understand the benefit/risk in the context of what can be implemented.	
	What is the overall quality of this evidence for the critical outcomes?	Efficacy of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Moderate* ☒ *High* ☒ Safety of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☒ *Moderate* ☐ *High* ☐	GRADE high quality evidence for the short term efficacy following three doses of the vaccine on the critical outcome of severe malaria occurring at >12 months. Moderate quality evidence on the need for the 4th dose to prevent severe malaria occurring at >12 months. Low quality evidence on the safety of the intervention on the outcome of serious adverse events (meningitis and non-meningitis).	

VALUES & PREFERENCES	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	Pilot implementation projects need to confirm the limited existing evidence that this malaria vaccine in principle would be acceptable to the target population. It would be assumed that there is a strong public desire to reduce malaria cases, particularly severe and life-threatening malaria in children. It remains to be assessed whether the 4th dose is acceptable to the target population as the balance of the positive impact and the potential negative safety issues may shift if only 3 doses are administered. There is a public health interest in having additional child health visits for a range of interventions, and new RTS,S vaccination visits could help to facilitate these additional contacts.	

RESOURCE USE	Are the resources required small?	*No* ☒ *Uncertain* ☐ *Yes* ☐ *Varies* ☐	Resources will be required for commodity procurement and for the health system. Resources will be required for adding new vaccination visits (at least 1 for first 3 doses and an additional visit for 4th dose). GSK has committed to at-cost (plus 5%) pricing. Malaria prevention/control funds are allocated to proven interventions; there should be no diversion of funds from existing measures.	
	Cost-effectiveness	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	Predictions of RTS,S/AS01 cost-effectiveness per DALY averted are comparable with other new vaccines. Four mathematical models of the impact of RTS,S/AS01 predict a substantial additional public health impact of RTS,S in settings with prevalence of infection in those aged 2-10 years between 10% and 65%. In the moderate to high transmission settings, median predictions range from 200 to 700 deaths averted per 100,000 vaccinees in a schedule with a fourth dose, and 10% to 28% of all malaria deaths averted in vaccinated children less than five years old. 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	It needs to be ensured that resources are not diverted from other proven malaria preventive interventions to the vaccine.

			coverage of seasonal malaria chemoprevention, where the latter intervention is appropriate. However the model predictions should be interpreted cautiously as the models were not able to replicate the rebound in severe disease observed in the phase 3 trial.	
EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Uncertain* ☐ *Reduced* ☒ Varies ☐	Equity within countries between malarious and non-malarious areas as well as equity between countries could be improved through reduction of morbidity and mortality due to malaria in Sub-Saharan Africa, a disease of the poor with substantial economic consequences.	
ACCEPTABILITY	Which option (intervention: RTS,S/ASO1 vaccine plus other preventive measures vs comparison: other preventive measures only) is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	It is likely that the RTS,S/ASO1 vaccine would be acceptable to key stakeholders if support is provided to cover the costs of the vaccine program and/or cost of the vaccine is low enough to be funded by countries themselves.	

	Which option is acceptable to target group?	*Intervention* ☐ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☒	It is likely that the RTS,S/AS01 vaccine would be acceptable to the target group if the costs are covered by the health care provider. It remains to be assessed whether the additional visits to the health care clinic are acceptable to the target population as extra visits also mean extra cost to caregivers who need to bring their children more often. For poor families, who are likely to benefit the most, this is a critical issue	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☒ *Probably Yes* ☐ *Yes* ☐ *Varies* ☐	Implementing the 4 dose schedule in the recommended age group may be challenging. Additional resources will be needed for immunization services. Families will need to make additional visits to vaccination clinics. Without administering the 4 fourth dose, there is no overall benefit on the efficacy of the vaccination. It may be challenging to communicate to caregivers that only 4 doses will have the desired effect.	

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)	WHO recommends that the staged pilot implementations use the 4-dose schedule of the malaria vaccine in 3-5 distinct epidemiological settings in sub-Saharan Africa, at subnational level, covering moderate-to-high transmission settings.				
Implementation considerations	These pilot implementations should be done in phased designs and in the context of ongoing high coverage of other proven malaria control measures, particularly long-lasting insecticidal nets (LLINs), access to rapid diagnostic tests (RDTs) and artemisinin-combination therapies (ACTs), and, where appropriate, seasonal malaria chemoprevention (SMC) . The pilot implementations should involve sufficiently large populations, followed for an adequate duration, with rigorous evaluation. Additional considerations for the choice settings of pilot implementations include the existence of Hib, pneumococcal conjugate and where relevant men A conjugate vaccination programmes. Prior to any pilot implementation, appropriate training and communication materials for the general public and for health workers should be developed and disseminated with particular emphasis on the incomplete protection conferred by the vaccine and hence the need to continue to use other malaria control measures and to seek health care promptly in the case of fever, the importance of ensuring the child receives all 4 doses of the vaccine.				

Monitoring and evaluation	Careful evaluation should be conducted to allow the: • Assessment of operational feasibility of providing the malaria vaccine in the target age-group at the recommended 4-dose schedule in the context of health service delivery in various countries; • Evaluation of the impact of the vaccine on child mortality, including measures to determine the impact of the vaccine when added to concomitant malaria interventions, by sex; • Surveillance for adverse events following vaccination, with an emphasis on meningitis and cerebral malaria including by sex and using standardized case definitions; • Systematic compilation of evidence on the functioning of the immunization programme, adherence to currently recommended malaria control measures, and broader health system functioning and community engagement, including evidence of any adverse effects of vaccine implementation on other malaria control measures.
Research priorities	• Evaluation of the efficacy of a fifth dose of RTS,S/AS01 administered one year after the fourth dose, and assessment of whether a fifth dose is needed to protect against a potential rebound in severe disease after the fourth dose, • Monitoring possible emergence of vaccine-resistant plasmodium strains following large scale use of the vaccine, • Exploration of alternative schedules and other strategies to improve the efficacy and safety of the RTS,S vaccine, • Clinical trial evaluation of the malaria vaccine in the context of elimination, including studies evaluating safety immunogenicity and efficacy against infection over a wide age range. A high priority area for such an evaluation is South-East Asia in areas of artemisinin resistance, • Impact of HIV infection on vaccine efficacy and duration of protection, • Impact of RTS,S vaccine deployment on the utilization of other malaria control interventions, • Impact of RTS,S vaccine deployment on coverage of other vaccines, • Evaluation of the impact of different communication strategies in terms of improving vaccine coverage and effectiveness.

[i] This Evidence to Recommendation table is based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel). http://www.decide-collaboration.eu/WP5/Strategies/Framework

[ii] Recommendations on the use of this malaria vaccine were discussed by SAGE and MPAC in October 2015; evidence presented at this meeting can be accessed at: http://www.who.int/immunization/sage/previous/en/index.html

[iii] Further evidence and references are provided in the WHO position paper "Malaria Vaccines: WHO position paper – January 2016".