BACKGROUND PAPER ON THE

RTS,S/AS01 MALARIA VACCINE

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Contents

1. Executive summary of JTEG's assessment and proposed recommendations

WHO provides member states with policy advice regarding introduction and use of new interventions. In developing and formulating policy recommendations, WHO considers factors in addition to the benefit-risk assessment performed by regulators, as well as important contextual elements such as the feasibility of implementation, in this case the effects of the vaccine in different transmission intensity settings, the value of the vaccine in the context of other malaria control measures, and the likely cost-effectiveness of the intervention in different settings.

A malaria vaccine has been evaluated in a large, multicentre Phase 3 trial, and key results from this trial were the basis for the proposed recommendations of JTEG. The trial showed that in both age groups evaluated (infants vaccinated at 6-12 weeks of age (vaccine efficacy (VE) over 18 months post dose 3, 26.6%) and a group vaccinated at 5-17 months of age (VE over 18 months post dose 3, 45.7%) there was moderate but potentially important protection against clinical malaria that declined to a low level by 18 months after the third dose. Protection was partially restored by a fourth dose, given 18 months after the third dose, after which there was also a rapid decline in efficacy (see Table 1.1 below, VEs over full duration of trial in the groups vaccinated at 6-12 weeks and 5-17 months of age were 26.7% and 39.0% respectively). The efficacy was substantially higher in the older age category compared to the younger age category. The public health impact of a malaria vaccine is mainly driven by any reduction in mortality conferred by vaccination. It was not possible to measure a reduction in deaths in the Phase 3 trial because of the sample size and close follow-up of the participants, with consequent earlier treatment of malaria than occurs outside trial settings. The best surrogate measure that could be measured to assess the likely impact on mortality was severe malaria, which was a secondary endpoint in the trial. Among those who received a fourth dose, there was demonstrated efficacy against severe malaria during the approximately 4 years of follow-up (median follow-up 48 months) in the group vaccinated at 5-17 months of age (VE 31.5%). Among those who did not receive a fourth dose, the initial protection against severe malaria was balanced by an excess of severe malaria in the later follow-up period such that overall there was no net reduction in the number of severe cases. In the younger age category protection against severe malaria was not demonstrated in children with or without a fourth dose.

Table 1.1: Vaccine efficacy (95% CIs) against clinical and severe malaria. Per protocol analyses.

Study period*	6-12 weeks		5-17 months	
	VE against clinical malaria	VE against severe malaria	VE against clinical malaria	VE against severe malaria
2.5M-14M	32.9% (26.3, 38.9)	38.5% (7.8, 59.0)	51.3% (47.5, 54.9)	44.5% (23.8, 59.6)
2.5M-20M	26.6% (20.3, 32.4)	17.4% (-16.2, 41.3)	45.7% (41.7, 49.5)	37.7% (18.0, 52.6)
2.5M-SE (3 doses)	18.2% (11.4, 24.5)	16.0% (-14.5, 38.4)	26.2% (20.8, 31.2)	-2.2% (-31.3, 20.4)
2.5M-SE (4 doses)	26.7% (20.5, 32.4)	20.5% (-9.8, 42.5)	39.0% (34.3, 43.3)	31.5% (9.3, 48.3)

*2.5M is 2 weeks after the third dose. Thus 20M is approximately 18 months after the third dose. SE (Study end) 6-12 weeks group: median 38 months after dose 1. SE (Study end) 5-17 months group: median 48 months after dose 1.
ITT results are not notably different to the above per protocol figures (Appendix 2).

In children in the older age category there was an excess risk of febrile seizures within 7 days after any of the vaccine doses. In children in the younger age category this excess risk was only apparent after the fourth dose. There were no long-lasting sequelae due to any of the febrile seizures.

In children in the older age category there was an increased number of meningitis cases in malaria vaccine groups compared to the control group. These meningitis cases were not temporally related to the timing of vaccine doses and there were a range of aetiologies in the cases identified. An excess of meningitis was not seen in children vaccinated in the younger age group. Whether this increase in meningitis was due to chance or represents a true adverse effect of the vaccine is unknown.

In children in the older age category there was an increased number of cerebral malaria cases in malaria vaccine groups compared to the control group. This finding was in a subgroup analysis and its significance in relation to vaccination is unclear. An excess of cerebral malaria was not seen in children vaccinated in the younger age group.

There is a need to evaluate initial introductions before wider scale-up is considered to address a number of issues that remain following the conclusion of the trial. The primary issues are:

- The extent to which the protection demonstrated in the Phase 3 trial could be replicated in the post-licensure phase because of the challenge of implementing four doses at the population level, including the need for new immunization contacts

- The safety signals of most concern (i.e. imbalances in meningitis and cerebral malaria) in the trial may be chance findings, but further evaluation is necessary when the vaccine is given to larger numbers of children

- The impact on mortality could not be assessed in the Phase 3 trial and as this is the main driver of the public health impact and cost-effectiveness of the vaccine, it is important to assess the mortality reduction following large-scale vaccination.

Based on the data from the Phase 3 trial, JTEG does not recommend the use of the malaria vaccine in the younger (6-12 weeks) age group. With respect to the older age group (5-17 months), JTEG recommends the initial introduction of 4 doses of the malaria vaccine in 3-5 distinct epidemiological settings in sub-Saharan Africa, likely at subnational level, to generate critical information on the issues described above (large demonstration projects). These settings should be selected such that

- they cover a range of moderate-to-high transmission settings, with at least one setting with strongly seasonal malaria transmission.

- it is possible to ascertain and diagnose cases of meningitis and severe malaria and record deaths.

- the population vaccinated should be of sufficient size to allow evaluation of the impact on mortality, probably through a phased introduction of the vaccine within the selected settings. It is likely that several hundred thousand vaccinated children will be included in each setting and that phased introduction would need to be randomized to ensure

comparability of vaccinated and unvaccinated groups. Each initial introduction will be a large demonstration project.

- there should be high existing coverage of other proven malaria control measures including LLIN (or IRS), access to RDTs and ACT, and SMC in highly seasonal areas.

JTEG strongly recommends that WHO oversees the design and evaluation of these phased introductions and monitors the emerging findings. If appropriate, SAGE and MPAC may broaden recommendations on the basis of these emerging findings.

JTEG notes that it would be appropriate for WHO to recommend countrywide introduction if concerns about safety have been resolved, and if favourable implementation data become available, including high coverage of the fourth dose.

As JTEG recommends introduction in 3-5 moderate-to-high transmission settings, where there is a significant burden of malaria in the first year of life, it is important to vaccinate at a young age within the 5-17 month age range. There is no evidence that vaccine efficacy varied according to the month of age at which vaccination was started within this age group. In the phased introduction of the vaccine, JTEG recommends a three dose initial series of the malaria vaccine with a minimum interval between doses of four weeks, followed by a fourth dose at 15-18 months following the third dose. It is encouraged that the first dose be initiated as close as possible to age five months and the third dose be completed by nine months of age, if possible. Co-administration has been evaluated with measles and DTP-containing vaccines and is considered acceptable.

Prior to any phased introduction appropriate communication materials should be developed and disseminated with particular emphasis on the partial efficacy of the vaccine and the importance of the fourth dose. Messages should include the importance of maintaining usage of non-vaccine malaria preventive measures and the likelihood that febrile episodes in vaccinated children may still be due to malaria.

Research recommendations

There are currently no data to support a fifth dose. Therefore, evaluation of safety and effectiveness of a fifth dose could be included in the proposed phased introductions.

JTEG recommends monitoring of the emergence of vaccine-resistant strains following widespread use of the vaccine.

JTEG recommends that there is further exploration of alternative schedules, including schedules adapted to highly seasonal settings, and other strategies to improve the efficacy of the vaccine.

JTEG recommends an exploration of how to capitalize upon the new immunization contacts for general improvements in child health, including increasing coverage with other vaccines.

JTEG recommends that there is an evaluation of the malaria vaccine in the context of elimination, including studies evaluating administration and effectiveness against infection over a wide age range. A high priority geographic area for such an evaluation is South-East Asia in areas of artemisinin resistance. ***For overall JTEG assessment, see section 10.***

2. Background

2.1 Epidemiology and disease burden of malaria

Based on 2013 data, WHO estimated that approximately 584 000 deaths per year were attributable to malaria, 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[1]. Most malaria deaths in Africa occur in children younger than 5 years. Adults who grew up in malaria endemic areas since childhood and remain resident in such areas are generally not at risk of death from malaria. The number of new episodes of clinical malaria in 2013 was estimated to be 198 million (uncertainty range 124-283 million). Infants and young children in malaria-endemic countries in Africa typically experience several clinical episodes of malaria before they accumulate partial immunity, which protects against severe disease and death from malaria. They accumulate immunity to febrile malaria more gradually during childhood and, generally by adulthood, acute episodes of febrile malaria are infrequent. The economic costs of malaria between 1980-1995 in heavily affected countries have been estimated to have been 74 billion USD, and the disease has been estimated to reduce gross domestic product by several percentage points[2].

In most African countries substantial malaria-control efforts have been implemented, including the widespread deployment of long-lasting insecticide-treated bed-nets (LLIN), the use of indoor residual spraying of insecticide in some settings, prompt diagnosis using quality assured rapid diagnostic tests (RDTs) and by using highly effective artemisinin-combination therapies (ACTs). In many settings, these measures are considered to have reduced the annual incidence rates of new malaria cases and malaria deaths by 50% or more since 2000[1, 3] and the geographic area with very high prevalence of malaria has been substantially reduced (Figure 2.1). While economic development and other factors may also have played a role in reducing the malaria burden, much of the decrease is likely attributable to large scale deployment of highly cost-effective interventions supported by over 10-fold increase in financing for malaria control over the last 10-15 years.

In different areas of Africa, malaria parasite transmission may occur throughout the year or be strongly seasonal, determined largely by rainfall patterns. The intensity of transmission generally varies as a function of vector man biting rate and vector survival, which is strongly influenced by temperature and humidity, as well as vector control measures. Because of variations in climatic factors and the availability of vector breeding sites, malaria parasite transmission may be very heterogeneous within a country. For example in parts of western Kenya malaria parasite transmission is very high, and malaria remains a prominent cause of childhood mortality, whereas in some other parts of Kenya there is currently little or no malaria parasite transmission.

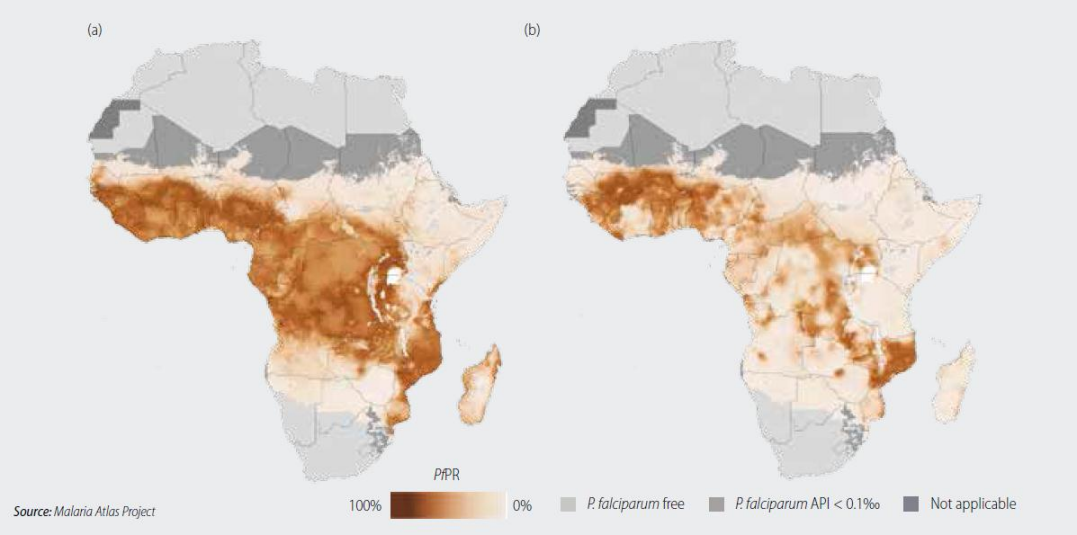


Figure 2.1: Estimated proportion of children aged 2-10 years infected with *P. falciparum* in a) 2000 and b) 2013[1].

A measure of the intensity of malaria parasite transmission is given by the entomological inoculation rate (EIR), which is the estimated number of times that an individual is bitten by an infected mosquito in a year. In different malaria-endemic areas the average EIR may range from in excess of 1000 to less than 1. In areas of very high transmission (i.e. an EIR of 100 or more), most children will have detectable parasites in their blood most of the time. Over the last decade or more the number of such highly infected areas in Africa has reduced substantially due to scaled up malaria control measures.

Acquired immunity to malaria, through repeated infections, may be relatively short-lived in the absence of exposure to natural boosting. Thus persons who leave a malaria endemic area for an extended period (e.g. a year) may be susceptible to severe disease if they are reinfected on return to an endemic area. Similarly, in areas where transmission is irregular and varies greatly from year to year, clinical immunity is difficult to acquire and may be largely lost during a prolonged period when transmission is low, making all age-groups at risk of developing severe malaria.

The frequency of episodes of malaria and the nature of disease due to malaria vary, depending on the age of the individual, and the intensity and seasonality of malaria parasite transmission. Morbidity due to infection with *P. falciparum* can range from a mild febrile illness, which is quite difficult to distinguish from many other similar illnesses, to fulminant and life-threatening disease with severe stupor and coma, or respiratory distress, or severe anaemia or a shock syndrome requiring immediate parenteral treatment, blood transfusions, fluid therapy and supportive measures, often in combination; the distribution of clinical manifestations varies by age as a function of transmission intensity (Figure 2.2). With repeated exposure protection is acquired, first against severe malaria, then against illness with malaria, and, much more slowly, against microscopy-detectable parasitaemia. Some clinical manifestations of malaria, such as cerebral malaria, occur more frequently in older children in both settings when transmission is seasonal or perennial, whereas severe life-threatening anaemia tend to occur in younger age-groups and is more prevalent where malaria parasite transmission is very intense and year-round. Furthermore, especially in

children and non-immune adults the clinical picture can change within 24 hours, from an illness that appears to be relatively mild to a life-threatening disease.

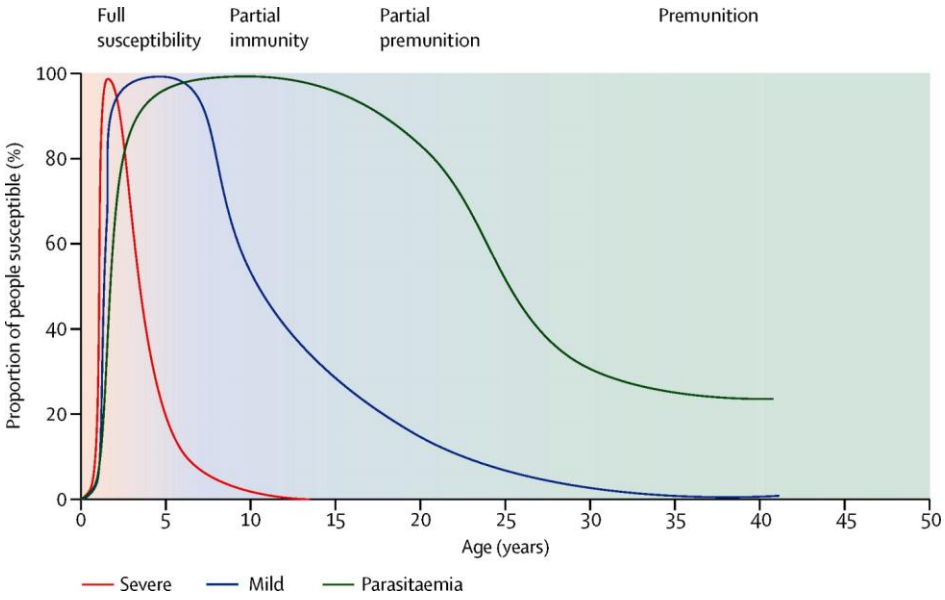


Figure 2.2: Relation between age and malaria severity in an area of moderate transmission intensity. From White *et al.* 2014[4].

2.2 Malaria Parasites and Pathogenesis

Five species of the *Plasmodium* protozoan parasite have been identified which can infect humans (*P. falciparum, P. vivax, P. ovale, P. malariae* and *P. knowlesi*). With the exception of *P. knowlesi*, humans are the only known reservoirs of these parasite species (*P. knowlesi* infects long tailed macaques and transmission to humans occurs in some parts of South-east Asia). However, *P. falciparum* accounts for more than 90% of all malaria-attributable deaths. *P. vivax* accounts for much of the remaining disease burden and is the dominant *Plasmodium* species in many areas outside of sub-Saharan Africa. Vaccine development efforts have focused on *P. falciparum* and, to a lesser extent, on *P. vivax*[5]. Human infection with the malaria parasite is established following the injection of the sporozoite form of the parasite by female anopheline mosquitoes; subsequent development occurs over 5-10 days through the liver stage, which is followed by the replication of parasites in red blood cells, causing symptoms, including fever. Morbidity and mortality from malaria may arise from: sequestration of infected red blood cells, severe anaemia due to red blood cell dysregulation and lysis, inflammation-related brain pathology, lactic acidosis, and a general shock-like syndrome with hypotension, hypoglycaemia and poor tissue perfusion.

2.3 Immune response to malaria infection

After repeated exposure to *P. falciparum* malaria infections, individuals develop a significantly reduced risk of developing serious illness or dying from subsequent malaria parasite infections. This acquisition of immunity through natural exposure occurs first to severe malaria and death, and much more slowly to milder clinical features of malaria such as fever. While immunity to patent parasitaemia, as detected by microscopy, does occur by adulthood after many exposures, subpatent

infections, detectable by molecular techniques, may still occur and it is unclear whether or not sterile immunity is acquired by some individuals after repeated infections. In areas of moderate-to-high transmission, malaria mortality begins to drop by around the age of 2 years, with the incidence of acute febrile malaria dropping later in childhood or adolescence. The mechanisms underlying naturally acquired immunity are not fully understood; however, there are two leading hypotheses. One is that the gradual acquisition of strain-specific immunity occurs; the other is that repeated antigenic exposure, perhaps in conjunction with an age-related immune maturation, is necessary for the development of immunity. Additionally, the immunity acquired during childhood does not protect primigravid women, thus accounting for an increased risk in malaria-attributable deaths in these women. Severe malaria in primigravid women is known to be mediated by sequestration based on binding of malaria parasites to placental ligands only present in pregnancy. Naturally acquired immunity is generally believed to wane to a significant degree if an individual migrates out of a malaria-endemic region and ceases to have regular exposure to malaria parasite infection for a number of years. Severe malaria illness can occur in people who have migrated out of, and then have returned to, a malaria-endemic area[6]. It remains a questions for research whether case fatality of severe malaria is as high in the malaria-exposed after a period without ongoing exposure, compared to the truly malaria naïve. Significant roles for both humoral and cell-mediated effectors have been demonstrated in animal models, and both humoral and cell-mediated immune responses have been induced in humans after natural malaria infection and exposure to experimental malaria vaccines. No clear correlates of protection have been established for vaccines, although an accumulating body of evidence indicates that antibodies to circumsporozoite protein (CSP) show some correlation to protection against the pre-erythrocytic stages of the parasite[7].

The development of protection against severe disease after natural malaria infection, and the possible role of identifiable and quantifiable effector mechanisms of protection, both lend a positive perspective to the development of effective malaria vaccines. However, the complexity of the parasite and the highly complex genome with over 5,000 genes pose significant challenges.

2.4 Other malaria control measures

As noted above, there has been a resurgence of funding for malaria vector-control programmes, RDTs and ACTs. On World Malaria Day 2015 WHO drew attention to the major gains associated with the improvements in malaria control with malaria mortality estimated to have reduced by over 50% in WHO AFRO since 2000[1]. At the same time WHO highlighted the ongoing critical gaps in access to preventive, diagnostic and treatment measures. Many individuals and communities still do not have access to LLINs, RDTs and ACTs and WHO has called for an urgent scaling up of existing control measures. LLINs have been shown to cause a reduction in childhood mortality in randomised controlled trials. A Cochrane Review estimated 50% efficacy of ITNs against uncomplicated malaria episodes and 17% efficacy of ITNs against all-cause under five mortality (compared to no nets) in areas of high transmission[8]. Indoor Residual Spraying with insecticide is the predominant vector control method in some settings, and can be associated with marked reductions in malaria parasite transmission. In some countries IRS is deployed together with ITNs for malaria control, and in other countries it is mainly reserved for prevention and control of epidemics. The WHO African Region has the highest proportion of the population at risk protected by IRS: in 2013, 55 million people were protected, representing 7% of the population at risk. To prevent malaria in pregnant women and

newborns, WHO recommends Intermittent Preventive Treatment of malaria in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP), delivered at each scheduled ANC visit after the first trimester. In 2013 among nine reporting countries a median of 17% of all pregnant women received three or more doses of IPTp, in line with WHO recommendations. Seasonal malaria chemoprevention (SMC), previously referred to as Intermittent Preventive Treatment in children (IPTc), is defined as the intermittent administration of full treatment courses of an antimalarial medicine during the malaria season (typically monthly during the transmission season, for a maximum of four doses) to prevent malarial illness with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial risk. It reduces incidence of malaria (including severe malaria) by 75%. Since 2012, WHO has recommended SMC in areas of highly seasonal malaria parasite transmission across the Sahel sub-region, where an estimated 25 million children aged 3-59 months could benefit from this intervention every year[9].

2.5 Malaria vaccines

2.5.1 Malaria vaccine targets

The pre-erythrocytic stages (stages 1 and 2 in Figure 2.3) encompass the injection of the sporozoite stage of the parasite by the bite of an infected female anopheline mosquito, and the rapid homing of the sporozoite into the liver cells within a matter of minutes to a few hours. Antigens present on the surface of the sporozoite, such as circumsporozoite protein (CSP), or deployed to the surface of the infected hepatocyte, have been used as pre-erythrocytic-stage candidate vaccines. Immune responses directed at either the sporozoite stage or at the infected hepatocyte could, in theory, prevent the blood-stage infection from developing. CSP (the antigen included in RTS,S) is the predominant surface antigen of the sporozoite and antibodies to CSP have been shown to prevent sporozoites migrating to and infecting hepatocytes. The rest of this section is not relevant to RTS,S, but is provided for completion.

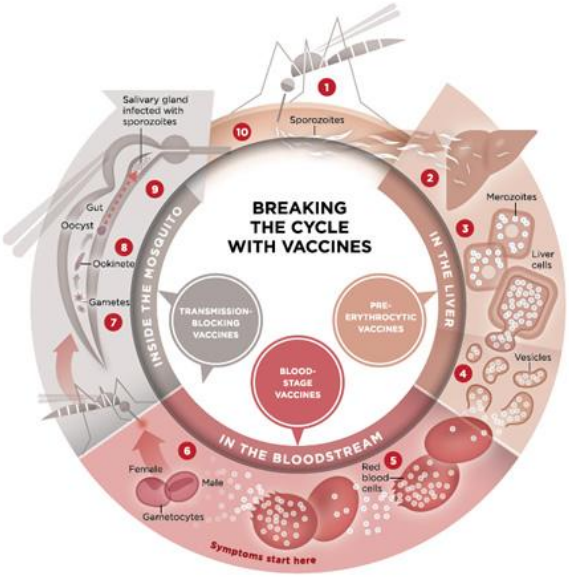


Figure 2.3: Malaria life cycle and associated vaccine targets (Figure by PATH Malaria Vaccine Initiative)[10].

Numerous antigens that are unique to either the merozoite (e.g. the merozoite surface antigens) or to the infected erythrocyte (e.g. erythrocyte-associated surface antigens) are potential erythrocytic-stage vaccine antigens, and such vaccines would either prevent the invasion of the erythrocyte by the merozoite, or would target the infected erythrocyte for destruction by the host's immune system. The net effect of such erythrocyte-stage immune responses could be to limit or ameliorate the blood-stage manifestations of the malaria parasite infection. Small subsets of infected erythrocytes undergo a developmental switch into the sexual stage of the organism, termed gametocytes. Gametocytes develop into extracelluar gametes in the midgut of the mosquito vector when taken in a blood meal

from an infected person to undergo fertilisation and continue development in the mosquito. Although most gametocytes remain within the host erythrocyte until they are taken up during a blood meal ingested by a female anopheline mosquito, some of the infected erythrocytes rupture in the host's reticuloendothelial system and present gametocyte-specific antigens to the host's immune system. Vaccines targeting gametocyte stages of the parasite, or targeting gametes and the post fertilization stage – the zygotes and subsequent ookinetes, which are found only in the mosquito midgut after fertilization occurs, may provide transmission-blocking immune responses that could interrupt transmission of the parasite from an infected person to an uninfected person by preventing development of a mature sporozoite in the mosquito. Combination vaccines containing antigens expressed at different stages of the parasite's life-cycle may induce an immune response with a broad biological effect.

2.5.2 Malaria vaccine pipeline

More than 30 *P. falciparum* malaria-vaccine projects are at either advanced preclinical or clinical stages of evaluation (Figure 2.4)[11]. Approaches that utilize recombinant protein antigens and target blood stages are being developed, but only RTS,S/AS01 (a pre-erythrocytic stage vaccine) has completed pivotal phase III evaluation and reached the regulatory review stage.

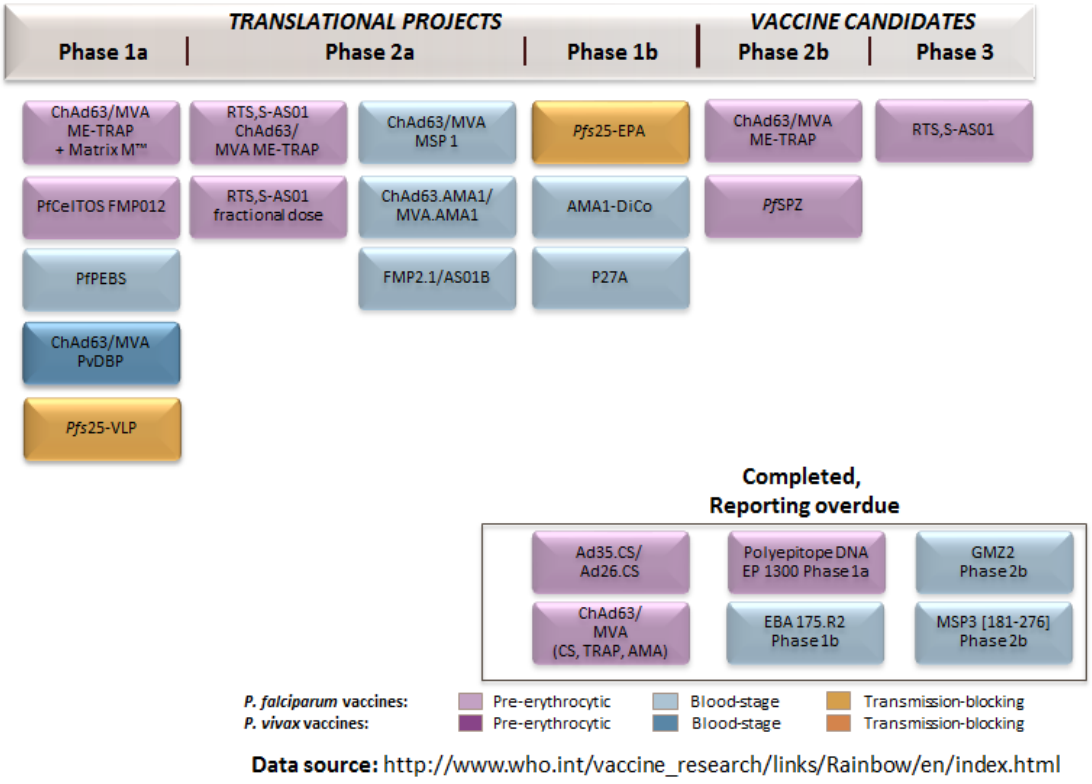


Figure 2.4: Global malaria vaccine pipeline Sep 2015.

Four other approaches have been tested in Phase 2b trials with several hundred volunteers each. These are ChAd63/MVA ME-TRAP, MSP3, GMZ2 and PfSPZ. ChAd63/MVA ME-TRAP uses two different recombinant viral vectors to induce T cell responses to the liver stage antigen TRAP. GMZ2 is a recombinant protein approach based on a fusion of two blood stage antigens. Both the ME-TRAP and GMZ2 programmes have enrolled hundreds of volunteers in multiple trials across Africa. MSP3, another blood stage antigen, has mainly been tested in Mali. Efficacy results against clinical malaria

in children have not been reported for any of these trials. Whole parasite vaccines are under development. In one of these vaccines, known as PfSPZ, sporozoites are attenuated by irradiation while still in the mosquito's salivary gland and there is subsequent extraction of irradiated sporozoites by dissection of the salivary glands of these irradiated mosquitoes. Other whole-organism approaches to malaria immunization are being explored using various methods, including genetic attenuation of sporozoites. In addition to the approaches outlined above there are many others in clinical evaluation or at an advanced stage of pre-clinical evaluation[12].

The most advanced candidate is the vaccine against *P. falciparum* malaria disease known as RTS,S/AS01, and is the focus of this background paper. This vaccine, which is based on the *P. falciparum* sporozoite antigen CSP, was developed after a series of clinical trials demonstrated that simpler CSP-based vaccines provided inadequate clinical efficacy. Furthermore, in addition to using a novel delivery system based on the hepatitis B–malaria antigen fusion protein, novel adjuvants have been utilized because RTS,S formulated on aluminium-containing adjuvants alone afforded no protection in human-challenge studies[13]. Various RTS,S/adjuvant formulations have been compared in human-challenge studies, and the formulation designated as RTS,S/AS01 appeared to provide the greatest protection[14].

As RTS,S/AS01 only contains CSP malaria antigen, the only possible biological action of the vaccine is at points 1 and 2 in figure 2.2. This results in either completely preventing an incident liver-stage infection, reducing the numbers of sporozoites infecting hepatocytes after an infective bite, or inhibiting liver-stage development either completely or partially. CSP is not expressed in the blood stage, and so RTS,S/AS01 immune responses do not directly affect the blood stages of the life cycle.

3. RTS,S Overview, including Phase 3 Trial Design

3.1 History of RTS,S Development

Extensive research beginning in the 1960s, indicated that immunization with radiation-attenuated sporozoites could protect animals and human volunteers from malaria parasite infection[15, 16]. The circumsporozoite protein (CSP), a sporozoite surface antigen, was identified as a possible target of protective immune responses, and the gene encoding the CSP of *Plasmodium falciparum* was cloned and sequenced[17].

In early 1984, The US Walter Reed Army Institute of Research (WRAIR) entered into a collaboration with GSK to produce a malaria vaccine using recombinant *E. coli* expression systems. Although efforts to produce a full-length CSP were unsuccessful, a series of alternative constructs were produced. Studies using synthetic peptides had mapped the epitope of protective monoclonal antibodies to the central repeat region of the *P. falciparum* CSP, and several constructs were developed with iterative clinical testing using challenge studies in naive adult volunteers; none proved sufficiently efficacious to take forward.

In 1987, the GSK malaria vaccine program was transferred from its laboratories in Philadelphia, PA, to its vaccine division in Belgium. None of the previous iterations of CSP-based vaccines in the GSK and other malaria vaccine programmes had used a particulate structure. In 1988 details of the first generation particulate CSP-based construct were published[18]. This was followed by the first

publication of a clinical trial using the CSP-Hepatitis B surface antigen fusion particulate structure present in RTS,S[19]. While the particle was a major step forward above the earlier peptide iterations, novel adjuvants were also an important aspect. RTS,S formulated on alum yielded no protection in the human challenge model, whereas formulations using the adjuvant AS02 proved reproducibly efficacious in the challenge model[20]. RTS,S/AS02 was seen as the lead GSK candidate until RTS,S/AS01 was selected for use in the Phase 3 programme in 2009 on the basis of clinical efficacy seen in human challenge trials, together with improved immunogenicity[14]. The RTS,S program has been conducted as a public-private partnership between GSK and the Malaria Vaccine Initiative at PATH since 2001, and is a leading example of this type of public-private partnership approach.

On July 23, 2015, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive scientific opinion under Article 58 of Regulation (EC) No 726/2004[21].

3.2 Technical specifications

RTS,S is a pre-erythrocytic stage hybrid recombinant protein vaccine. It is comprised of the central tandem repeat and carboxyl terminal portion of the *P. falciparum* circumsporozoite protein fused to the hepatitis B surface antigen, co-expressed in yeast with non-fused hepatitis B surface antigen. RTS,S virus-like particles form when the RTS malaria–hepatitis B fusion protein is co-expressed with S antigen alone in *Saccharomyces cerevisiae* yeast cells. The formulation given a positive scientific opinion by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) is 25µg of RTS,S with AS01 as adjuvant, composed of liposomes and the immunomodulatory molecules 3-O-desacyl-f4-monophosphoryl lipid A (MPL) and QS-21. The adjuvant is specifically $AS01_E$ (in contrast to $AS01_B$, which is the formulation used in GSK's Herpes Zoster vaccine that has recently completely Phase 3 trials and contains two times more MPL & QS-21 immunoenhancers in the same liposomal suspension). The reconstituted 0.5mL vaccine is administered by intramuscular injection into the antero-lateral thigh in the 6-12 weeks age group, and the left deltoid in the 5-17 months age group. It has been evaluated most on a 0/1/2 month schedule (including Phase 3 trial). In the pivotal Phase 3 trial, the fourth RTS,S dose was given 18 months after the 3rd dose in the left deltoid. The WHO Programmatic Suitability for Prequalification (PSPQ) Standing Committee confirmed the suitability of the proposed 2-dose vial presentation.

3.3 Available data on RTS,S/AS01 and RTS,S/AS02

Prior to launching the Phase 3 efficacy trial, numerous studies were undertaken using RTS,S/AS02 or RTS,S/AS01 in different age groups, including adults (Appendix 1). Excluding the pivotal Phase 3 trial (Mal-055), RTS,S/AS01 has been given to 1,581 children aged 6 weeks to 17 months, including with various schedule and co-administration regimens, as well as HIV-infected children (Table 3.1).

Table 3.1: Overview of studies with RTS,S/AS01E in the target population of children 6 weeks-17 months at first dose. Provided by PATH-MVI on request.

Trial *Status year*	Objective(s)	Trial Design *Schedule*	Trial population Age *Country*	Trial groups	TVC N	Publication(s)
Malaria-047 *Completed 2008*	1°: Safety of two vaccine formulations according to various immunisation schedules 2°: Safety and immunogenicity	Phase II, partially blind (blind to vaccine administration, open to vaccination schedule), randomized (1: 1: 1: 1: 1: 1), controlled, multi-centre trial with six groups *0-1 months* *0-1-2 months* *0-1-7 months*	Healthy male and female children 5 - 17 months *Ghana*	RTS,S/AS01$_E$, 0-1, 25µg/0.5ml RTS,S/AS02$_D$, 0-1, 25µg/0.5ml RTS,S/AS01$_E$, 0-1-2, 25µg/0.5ml Rabies vaccine, 0-1-2[a] RTS,S/AS02$_D$, 0-1-2, 25µg/0.5ml [b] RTS,S/AS01$_E$, 0-1-7, 25µg/0.5ml RTS,S/AS02$_D$, 0-1-7, 25µg/0.5ml	90 90 90 45 45 90 90 **540**	Owusu-Agyei 2009 Ansong 2011
Malaria-049 *Completed 2008*	1°: Efficacy against clinical disease 2°: Safety and immunogenicity	Phase IIb, double-blind, randomized (1:1), controlled, multi-centre, multi-country trial with two groups *0-1-2 months*	Healthy male and female children 5 - 17 months *Tanzania, Kenya*	RTS,S/AS01$_E$, 25µg/0.5ml Rabies vaccine	447 447 **894**	Bejon 2008 Lusingu 2010 Bejon 2011 Olotu 2011a Olotu 2011b Ndungu 2012
Malaria-050 *Completed 2009*	1°: Safety 2°: Safety and immunogenicity Expl.: Efficacy against clinical disease	Phase II, open, randomized (1:1:1), controlled, multi-centre, multi-country trial with three groups *0-1-2 months* *0-1-7 months*	Healthy male and female infants 6 - 10 weeks *Gabon, Ghana, Tanzania*	RTS,S/AS01$_E$, 0-1-2, 25µg/0.5ml RTS,S/AS01$_E$, 0-1-7, 25µg/0.5ml Control* * *Tritanrix-HepB*™/Hib (DTPw-HepB/Hib), either given alone (control) or co-administered to all groups at 6, 10, 14 weeks of age and measles and yellow fever at 9 months of age	170 170 171 **511**	Agnandji 2010 Asante 2011
Malaria-055 *Completed 2013*	1°: Efficacy against clinical disease 2°: Efficacy against severe disease; Role of booster; Efficacy against hospitalization and mortality	Phase III, double-blind, randomized (1:1:1), controlled, multi-centre, multi-country trial with three groups in two cohorts *0-1-2-20 months*	Healthy male and female infants and children 6 - 12 weeks and 5 - 17 months *Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, Tanzania*	<u>children 5-17 months of age:</u> RTS,S/AS01$_E$(R3R), 25µg/0.5ml RTS,S/AS01$_E$(R3C), 25µg/0.5ml Rabies vaccine(C3C)	2976 2972 2974 **8922**	Leach 2011 Vekemans 2011b Lievens 2011 Swysen 2011 The RTS,S Clinical Trials Partnership 2011

				infants 6-12 weeks of age*: RTS,S/AS01$_E$(R3R), 25μg/0.5ml RTS,S/AS01$_E$(R3C), 25μg/0.5ml MCC (C3C) * *Tritanrix-HepB*™/Hib (DTPw-HepB/Hib) + OPV to all groups at 6, 10, 14 weeks of age	2180 2178 2179 **6537**	The RTS,S Clinical Trials Partnership 2012 The RTS,S Clinical Trials Partnership 2014
Malaria-057	1°: Safety and immunogenicity of 7 schedules integrated with an EPI regimen	Phase II, open, randomized, controlled, single-centre, trial with seven groups *Birth-10 weeks-14 weeks* *Birth-10 weeks-26 weeks* *6weeks-10weeks-14weeks* *6weeks-10weeks-26weeks* *Engerix-B at birth-Birth-10 weeks-26 weeks* *10weeks-14weeks-26 weeks* *14weeks-26weeks-9months*	Healthy male and female infants *Malawi*	All received three doses of RTS,S/AS01$_E$, 25μg/0.5ml according to schedules listed. Recruited at 0-7 days of age.	**480**	
Malaria-058 *Completed 2013*	1°: Safety in HIV+ infants and children 2°: Safety and immunogenicity	Phase III, double-blind, randomized (1:1), controlled, multi-centre trial with two groups *0-1-2 months*	HIV infected male and female infants and children 6 weeks - 17 months *Kenya*	RTS,S/AS01$_E$, 25μg/0.5ml Rabies vaccine	99 101 **200**	Otieno 2014
Malaria-063 *Ongoing (estimated completion 2018)*	1°: Non-inferiority of anti-HBs immune response induced by RTS,S/AS01$_E$ compared to licensed *Engerix-B* 2°: Safety; Non-inferiority of vaccine response induced by pneumococcal conjugate or rotavirus vaccines when co-administered with or without RTS,S/AS01$_E$ in an EPI regimen; Lot-to-lot consistency of the anti-HBs immune response	Phase III, open, randomized (1:1:1:1:1:1:1:1:1:3:3), controlled, multi-centre, multi-country trial with eleven trial groups (five treatment groups) *0-1-2 months*	Healthy male and female infants 8 - 12 weeks *Burkina Faso, Ghana*	3 study groups with 3 lots of RTS,S/AS01$_E$, 25μg/0.5ml + CoAd (*Infanrix/Hib* + OPV + *Synflorix*) + *Rotarix* staggered 3 study groups with 3 lots of RTS,S/AS01$_E$, 25μg/0.5ml + CoAd (Infanrix /Hib + OPV + *Rotarix*) + *Synflorix* staggered 3 study groups with 3 lots of RTS,S/AS01$_E$, 25μg/0.5ml + CoAd (*Infanrix /Hib* + OPV) + staggered (Synflorix + *Rotarix*) 1 study group with *Engerix-B* + CoAd (*Infanrix /Hib* + OPV + Synflorix) + *Rotarix* staggered 1 study group with *Engerix-B* + CoAd (*Infanrix /Hib* + OPV + *Rotarix*) + *Synflorix* staggered	142 142 141 141 139 **705**	-
Malaria-061 *Completed 2012*	1°: Lot-to-lot consistency and non-inferiority of the anti-CS immune response induced by	Phase III, double-blind, randomized (1:1:1:1), multi-centre study with four groups *0-1-2 months*	Healthy male and female children 5 - 17 months *Nigeria*	RTS,S/AS01$_E$, lot 1, 25μg/0.5ml RTS,S/AS01$_E$, lot 2, 25μg/0.5ml	81 79 80	Umeh 2014

	RTS,S/AS01$_E$ (3 commercial scale lots pooled) compared to pilot scale lot of RTS,S/AS01$_E$ 2°: Safety and immunogenicity			RTS,S/AS01$_E$, lot 3, 25μg/0.5ml Control RTS,S/AS01$_E$, 25μg/0.5ml	80 **320**	

N= number of subjects

a The PCEC rabies vaccine was only used in one study centre, at Kintampo – KHRC, Ghana

b Enrolment occurred only at Kumasi – KCCR/SMS, Ghana

R3R: Children and infants to receive 3 doses of RTS,S/AS01$_E$ on a 0-1-2-month schedule + a fourth dose of RTS,S/AS01$_E$ at study month 20.

R3C: Children and infants to receive 3 doses of RTS,S/AS01$_E$ on a 0-1-2-month schedule + a dose of a meningococcal C conjugate vaccine (*Menjugate* [Novartis]) at study month 20.

C3C: Children and infants to receive 3 doses of a control vaccine** on a 0-1-2-month schedule + a dose of a control vaccine** at study month 20.

** Control vaccine for children 5-17 months of age: rabies vaccine (VeroRab™ [Sanofi Pasteur]) on a 0-1-2-month schedule + *Menjugate* at study month 20.

** Control vaccine for infants 6-12 weeks of age: *Menjugate* on a 0-1-2-month schedule + *Menjugate* at study month 20.

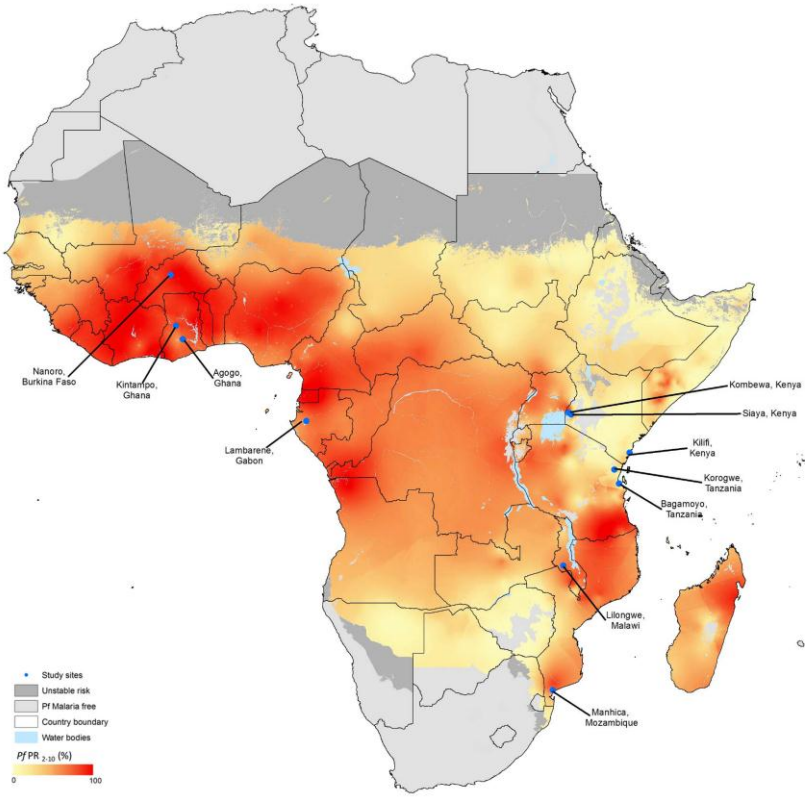


Figure 3.1: Trial sites and malaria endemicity - Adapted from Hay et al[22]. The location of each participating study site is shown on the spatial distribution of *P. falciparum* (Pf) malaria endemicity, modelled to reflect 2007 estimates. Malaria endemicity has changed since this time.

The Phase 3 efficacy trial was a randomized, controlled, multicentre, participant and observer-blinded trial (intervention and control vaccines differ in appearance, so study personnel who administered vaccines were aware of the treatment allocation; the unblinded vaccinators played no other part in the study)(NCT00866619)[23]. Participants in two age categories (5-17 months and 6-12 weeks at first vaccination) were enrolled between May 2009 and February 2011. A total of 6,537 6-12 week olds and 8,922 5-17 month-olds were randomized in the trial. The trial population was selected to represent the target population as much as possible, and low-birth-weight infants, malnourished children, and HIV-infected children who were not clinically unwell were included (participants were not systematically screened for HIV infection but some of the trial sites were in areas of high HIV prevalence). Participants were randomized 1:1:1 to receive control vaccine (C3C), three doses of RTS,S plus control vaccine at 18 months (R3C), or three doses of RTS,S plus a fourth dose of RTS,S at 18 months (R3R) (Figure 3.3). Control vaccines were the cell culture rabies vaccine (given to the 5-17 month age group for the first three doses) and meningococcal serogroup C conjugate vaccine (given to the 6-12 week age group for the first three doses, and to both age groups for the fourth dose). The 6-12 week age category received RTS,S/control co-administered with DTPwHepB/Hib + OPV for the first three doses, and OPV in addition to RTS,S or control vaccine as the fourth dose. The trial was designed to follow up participants for 32 months but was later amended to follow all participants until December 31, 2013, for a median follow up time of 48 months for 5-17 month olds and 38 months for 6-12 week olds. Seventy-eight percent of participants first vaccinated at age 5 – 17 months, and 92% of participants first vaccinated at age 6 – 12 weeks, were included in the per protocol populations[24].

Eleven sites in seven countries participated in the trial, representing different transmission settings (Table 3.2, Figure 3.1, Figure 3.2). These sites were selected to represent variable transmission intensities and seasonality patterns.

Details of the number of children included at different stages of the trial are shown in Figures 3.4 and 3.5.

Table 3.2: Overview of pivotal Phase III trial (MAL-055)

Ages included in trial	Two age categories: children at the age of 6-12 weeks (infants) and 5-17 months (children) at first vaccination.
Trial sites	11 centres in Burkina Faso (Nanoro), Gabon (Lambarene), Ghana (Kintampo and Agogo), Kenya (Kilifi, Kombewa and Siaya), Malawi (Lilongwe), Mozambique (Manhica) and Tanzania (Bagamoyo and Korogwe).
Treatment groups	Three treatment groups per age (1:1:1 randomization): • **R3R** received RTS,S/AS01$_E$ for four vaccinations • **R3C** received RTS,S/AS01$_E$ for three vaccinations and the control (MCC) for fourth vaccination • **C3C** received the control (Rabies for 5-17 month children and MCC for 6-12 week infants) for the first three vaccinations and the fourth (MCC for both age groups) vaccination
Dosing schedule	Doses are given on a 0, 1 and 2 months schedule, the fourth dose at 18 months after the 3rd dose.
Other vaccines administered	Infants receive Tritanrix HepB/Hib + OPV concomitantly with the first three doses and OPV concomitantly with the fourth dose. Additional vaccination with BCG, OPV birth dose, measles and Yellow Fever were given according to local EPI practice.
Follow up time	Vaccine efficacy and immunogenicity are measured over a median of 38 (6-12 week younger age category) or 48 (5-17 month older age category) months after the 3rd dose.
Primary objectives	Efficacy co-primary objectives: • To evaluate the protective efficacy of RTS,S/AS01$_E$ against clinical malaria disease caused by *Plasmodium falciparum* in African children whose age at first dose will be from 5-17 months. • To evaluate the protective efficacy of RTS,S/AS01$_E$ against clinical malaria disease caused by *Plasmodium falciparum* in African children whose age at first dose will be from 6-12 weeks and will receive vaccine in co-administration with DTPwHepB/Hib antigens (Tritanrix HepB/Hib) and OPV. For the co-primary objectives, duration of follow-up was 12 months after completion of the first three doses.

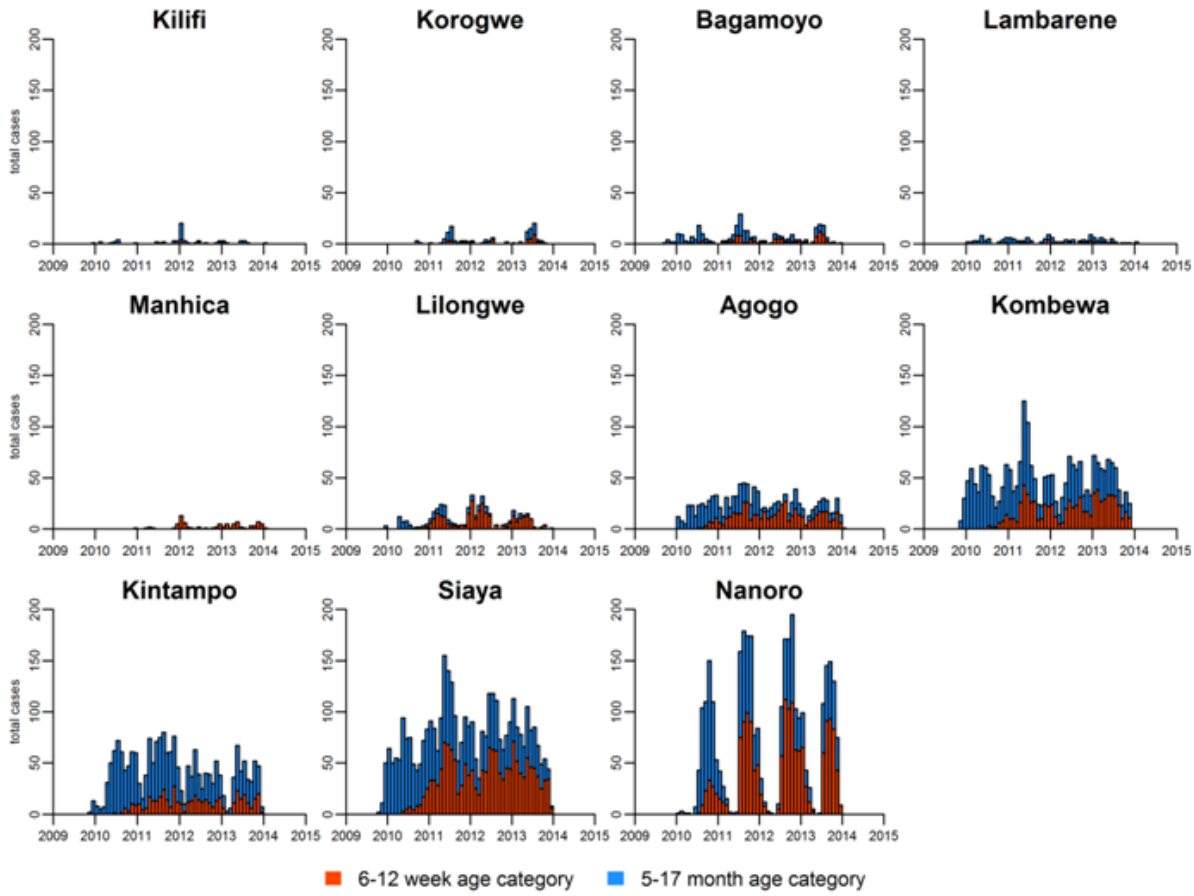


Figure 3.2: Total number of clinical malaria episodes in the control group at Phase 3 trial sites, indicating variation in incidence rate and seasonality profiles. Provided by GSK on request.

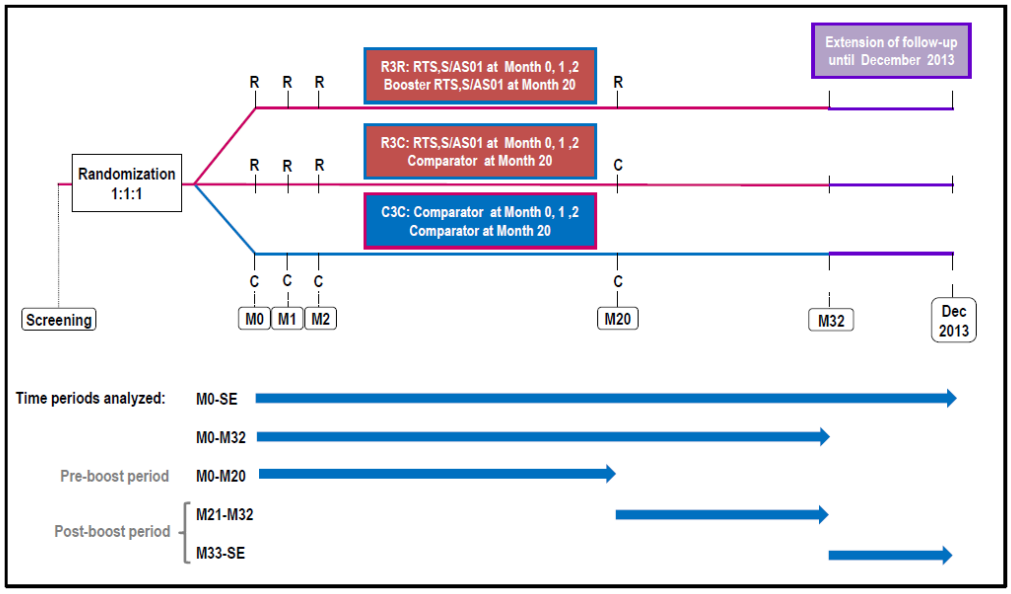


Figure 3.3: Phase III trial design[24].

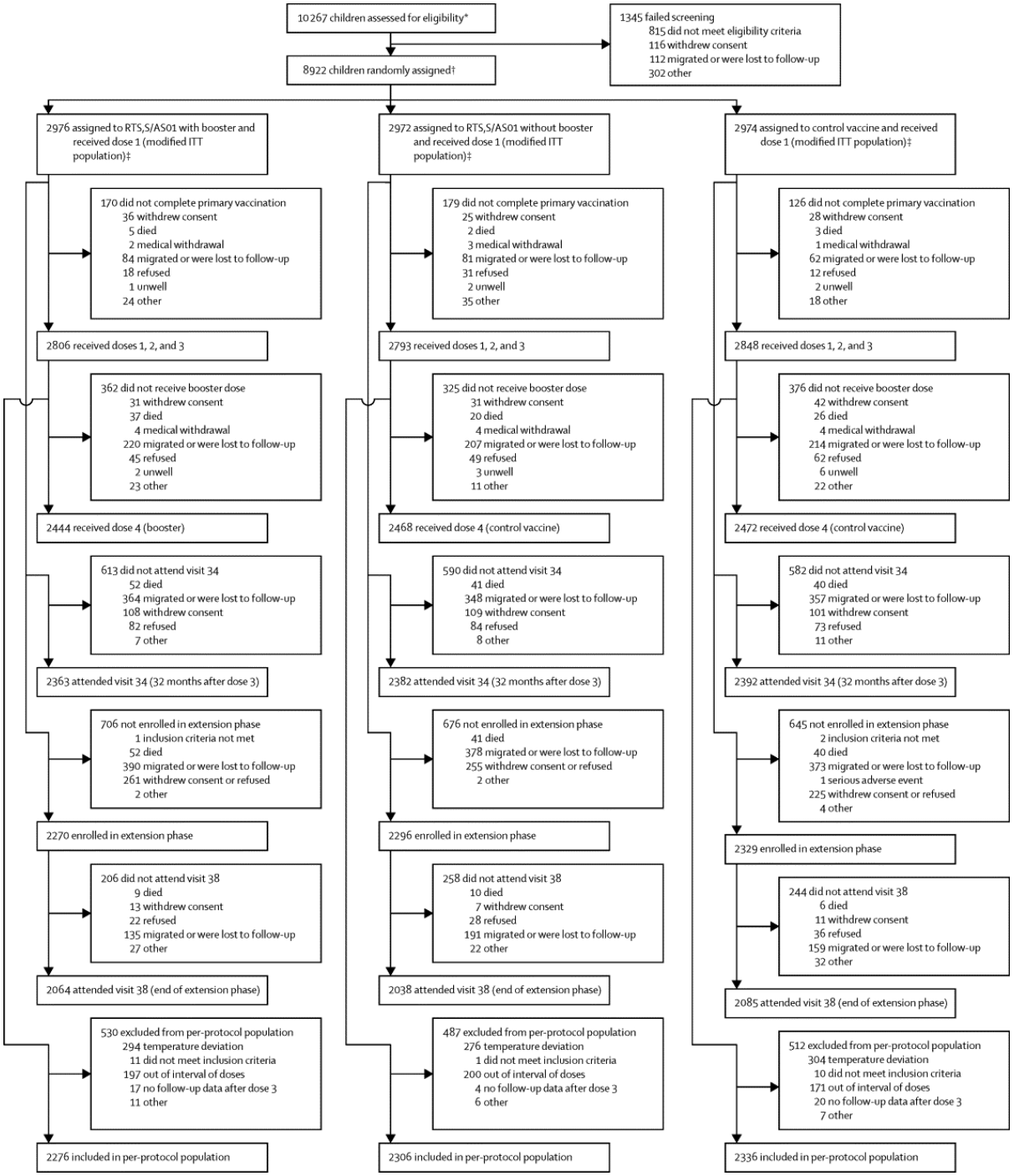


Figure 3.4: Consort diagram for 5-17 months age category[24].

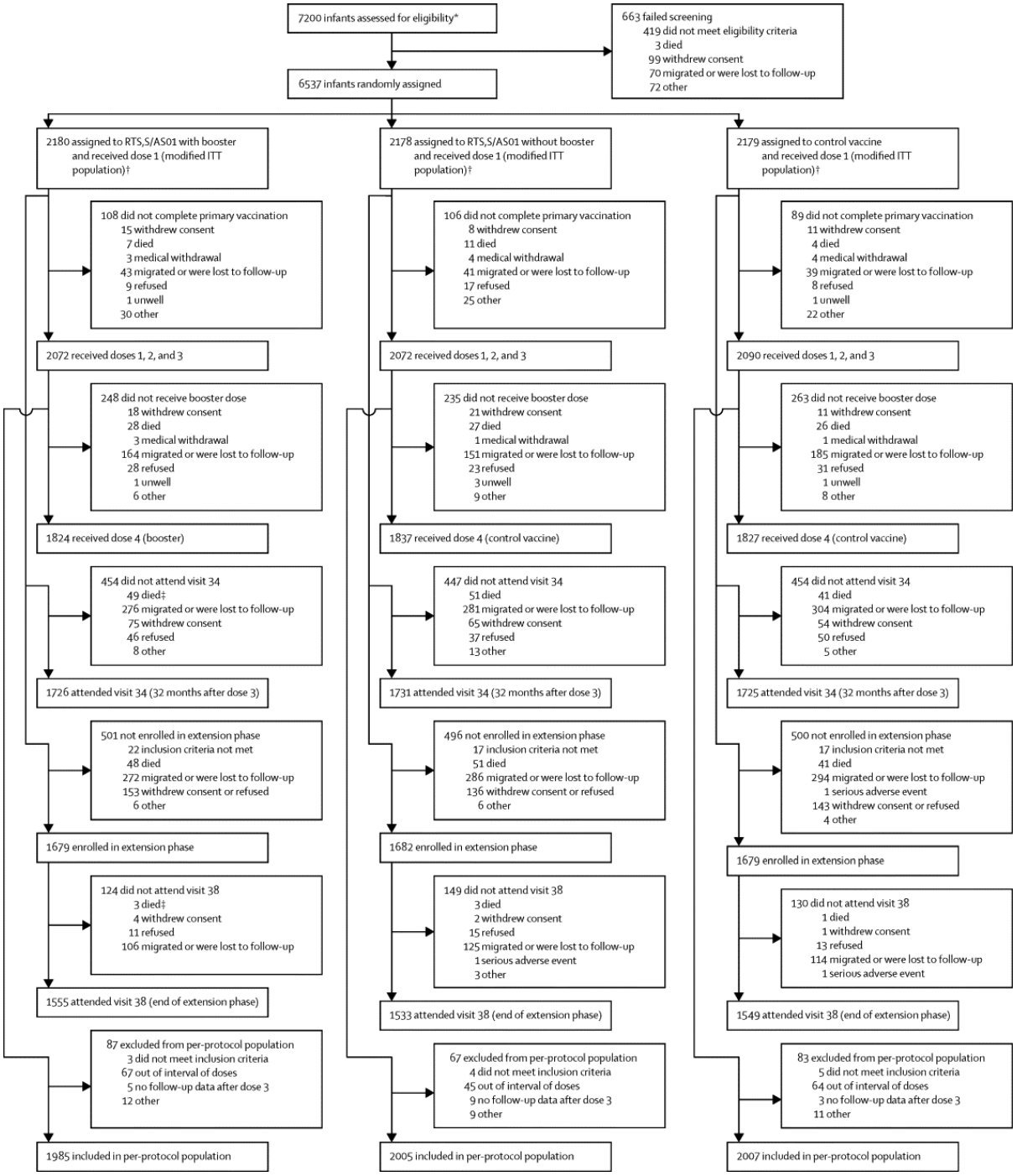


Figure 3.5: Consort diagram for 6-12 weeks age category[24].

4. RTS,S Vaccine Efficacy

4.1 Phase 3 trial efficacy objectives and case definitions

The co-primary objectives of the Phase 3 trial were efficacy over one year post-dose 3 against clinical malaria when administered in each of the two age categories. Clinical malaria cases were identified through passive surveillance at local health facilities. All participants were judged to have adequate access to health care, and health care costs were reimbursed by the trial. Among these children presenting at a health facility, the primary case definition for clinical malaria was >5,000 parasites/uL with an axillary temperature of $\geq$37.5^{o}C or a case that met the primary case definition for severe malaria. Reported efficacy estimates below are against all episodes of malaria, accounting for the fact that individual participants may have multiple episodes over the course of the trial. Vaccine efficacy against all episodes of malaria was assessed using a negative binomial regression with follow-up time as offset. Overall efficacy estimates were adjusted for site as a fixed effect; site-specific efficacy estimates were unadjusted. All vaccine efficacy estimates for Phase 2 and Phase 3 studies are according-to-protocol (ATP) unless otherwise specified. Representative intention-to-treat (ITT) analyses of vaccine efficacy may be found in Appendix 2. Safety analyses are always presented as ITT analyses.

Secondary objectives included vaccine efficacy against severe malaria, anaemia, malaria hospitalization, fatal malaria, all-cause mortality, and other serious illnesses. The 11 sites participating in the trial encompassed a range of malaria parasite transmission settings and there was also evaluation of efficacy by transmission setting and over time, and the effect of a fourth dose given at 18 months.

4.2 Vaccine efficacy against all episodes of clinical malaria

WHO/JTEG specifically requested all vaccine efficacies to be reported against all episodes of the outcome, not the first or only episode as is frequently presented in publications. The rationale for this approach is to better reflect the public health relevance of the vaccine. Readers should note that the estimates and figures presented in this background paper do not always match with cited figures from publications for this reason.

Tables 4.1 and 4.2 are summary tables of vaccine efficacy by age category and treatment group to different time points over the course of the trial. Figures 4.1 and 4.2 show the changing incidence by time, by treatment group. These represent important data that will be revisited throughout the background paper.

Table 4.1: Summary table of vaccine efficacy (95%CI) in the 5-17 month age category for all episodes of clinical malaria and severe malaria from Month 2.5 to selected time points (primary case definitions, ATP population).

Clinical Malaria	RTS,S Group				Control Group				VE (95%CI)
	N	n	T	n/T	N	n	T	n/T	
M2.5-M14	4553	2558	4035.9	0.63	2327	2489	2024.6	1.23	51.3% (47.5, 54.9)
M2.5-M20	4557	4257	6186.0	0.69	2328	3639	3100.4	1.17	45.7% (41.7, 49.5)
M2.5-SE 3-dose schedule	2306	6597	7335.8	0.9	2336	8352	7352.4	1.14	26.2% (20.8, 31.2)
M2.5-SE 4-dose schedule	2276	5691	7247.4	0.79					39.0% (34.3, 43.3)
Severe Malaria	**RTS,S Group**				**Control Group**				**VE (95%CI)**
	N	**n**	**T**	**n/T**	**N**	**n**	**T**	**n/T**	
M2.5-M14	4582	87	4358.3	0.020	2336	80	2219.3	0.036	44.5% (23.8, 59.6)
M2.5-M20	4582	129	6379.0	0.020	2336	105	3243.5	0.032	37.7% (18.0, 52.6)
M2.5-SE 3-dose schedule	2306	159	7600.5	0.021	2336	157	7664.8	0.020	-2.2% (-31.3, 20.4)
M2.5-SE 4-dose schedule	2276	101	7459.6	0.014					31.5% (9.3, 48.3)

N = number of subjects included in each group

n = number of episodes included in each group

T = person years at risk

n/T = Incidence = person year rate in each group

SE = Study end (variable follow up period for each participant with a median of 48 months)

VE (%) = Vaccine efficacy (Negative binomial random-effects model)

Sources for clinical malaria: M2.5-M14 and M2.5-M20, Table 1 and Suppl Table 15 in [25]; M2.5-SE, Suppl Table S7 in [24].

Sources for severe malaria: Provided by GSK on request.

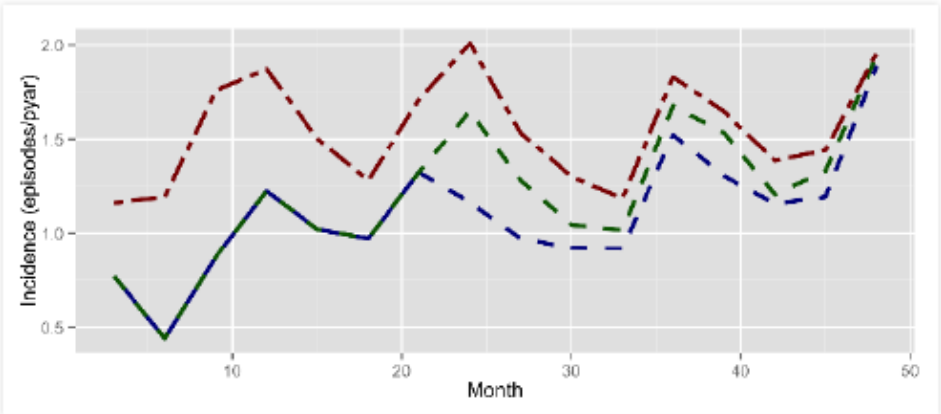


Figure 4.1: Incidence per year at risk (pyar) of clinical malaria after vaccination with three doses by study 3-month periods in 5-17 month age category. Red=C3C, Green=R3C, and Blue=R3R. Provided by J. Aponte.

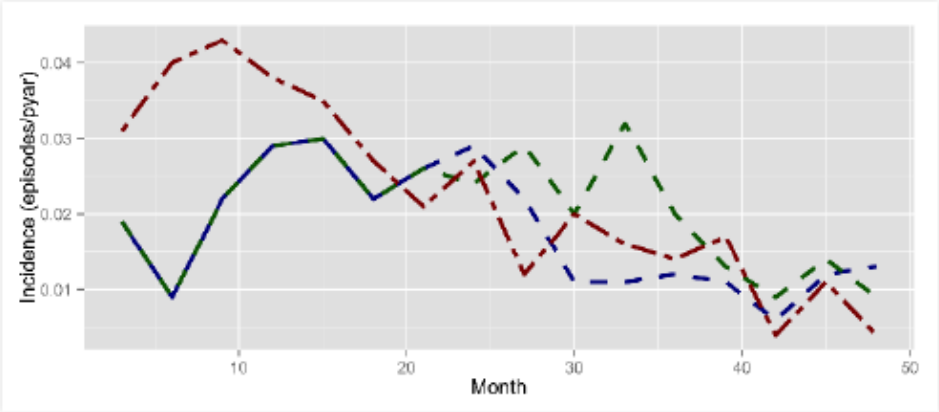


Figure 4.2: Incidence per year at risk (pyar) of severe malaria after vaccination with three doses by study 3-month periods in 5-17 month age category. Red=C3C, Green=R3C, and Blue=R3R. Provided by J. Aponte.

Table 4.2: Summary table of vaccine efficacy (95%CI) in the 6-12 weeks age category for all episodes of clinical malaria and severe malaria from Month 2.5 to selected time points (primary case definitions, ATP population).

Clinical Malaria	RTS,S Group				Control Group				VE
	N	n	T	n/T	N	n	T	n/T	(95%CI)
M2.5-M14	3995	2301	3604	0.64	2008	1626	1790	0.91	32.9% (26.3, 38.9)
M2.5-M20	3996	3848	5396.8	0.71	2007	2464	2674.0	0.92	26.6% (20.3, 32.4)
M2.5-SE 3-dose schedule	2005	5072	5322.9	0.95	2007	5666	5264.6	1.08	18.2% (11.4, 24.5)
M2.5-SE 4-dose schedule	1985	4532	5245.2	0.86					26.7% (20.5, 32.4)
Severe Malaria	**RTS,S Group**				**Control Group**				**VE**
	N	**n**	**T**	**n/T**	**N**	**n**	**T**	**n/T**	**(95%CI)**
M2.5-M14	3990	62	3791.8	0.016	2007	50	1895.7	0.026	38.5% (7.8, 59.0)
M2.5-M20	3990	112	5529.7	0.020	2007	68	2764.2	0.025	17.4% (-16.2, 41.3)
M2.5-SE 3-dose schedule	2005	103	5512.0	0.019	2007	121	5475.7	0.022	16.0% (-14.5, 38.4)
M2.5-SE 4-dose schedule	1985	96	5413.5	0.018					20.5% (-9.8, 42.5)

N = number of subjects included in each group
n = number of episodes included in each group
T = person years at risk
n/T = Incidence = person year rate in each group
SE = Study end (variable follow up period for each participant with a median of 38 months)
VE (%) = Vaccine efficacy (Negative binomial random-effects model)
Sources for clinical malaria: M2.5-M14, Table 1 in [26]; M2.5-M20, Table 2 in [25]; M2.5-SE, Suppl Table S17 in [24].
Sources for severe malaria: Provided by GSK on request.

4.2.1 VE against all episodes of clinical malaria: 5-17 months age category

Vaccine efficacy against all episodes of clinical malaria 12 months following the first three doses was 51.3% (95%CI 47.5, 54.9) across all sites (Table 4.1). Overall efficacy declined to 45.7% (95%CI 41.7, 49.5) by 18 months following the first three doses and to 26.2% (95%CI 20.8, 31.2) by the end of the trial, amongst participants who did not receive a fourth dose. The addition of a fourth dose 18 months following the first three doses increased the overall efficacy to 39.0% (95%CI 34.3, 43.3). The results did not substantially change with vaccine efficacy estimates based on secondary case definitions or with the ITT population (Appendix 2).

When vaccine efficacy was broken down by time interval[1], vaccine efficacy of three doses alone declined in successive six-month periods from 67.6% (95%CI 63.8, 71.0) initially, to 38.9% (95%CI 33.2, 44.0), 27.9% (20.2, 34.9), 13.9% (95%CI 4.7, 22.1), 12.5% (95%CI 1.1, 22.6), and finally to 0.1% (95%CI -9.9, 9.1) between 30 months following the first three doses and the end of the trial (Figure 4.3).

In the six months following the RTS,S/AS01 fourth dose in the R3R group, vaccine efficacy was estimated to be 42.9% (95%CI 36.4, 48.7). Thus efficacy is clearly increased when comparing R3R vs R3C in the period after the fourth dose, although not to the same level reported following the first three doses. Efficacy declines after the fourth dose with a similar timecourse to that seen after the third dose (Figure 4.3).

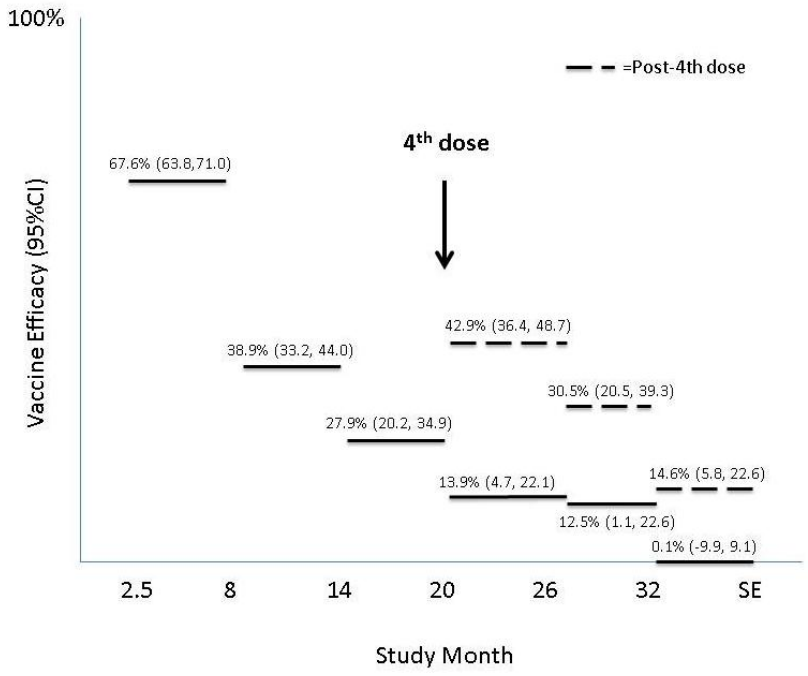


Figure 4.3: Vaccine efficacy against clinical malaria stratified by time period in the 5-17 month age category in the Phase 3 trial (primary case definition, ATP population). Data provided by GSK on request. Case counts available in Appendix 3.

Figure 4.1 shows the time-dependent incidence of clinical malaria among participants in the 5-17 month age category over the course of the trial. The variation in the difference between RTS,S and control groups remains throughout the course of the trial, with similar incidence rates in the three

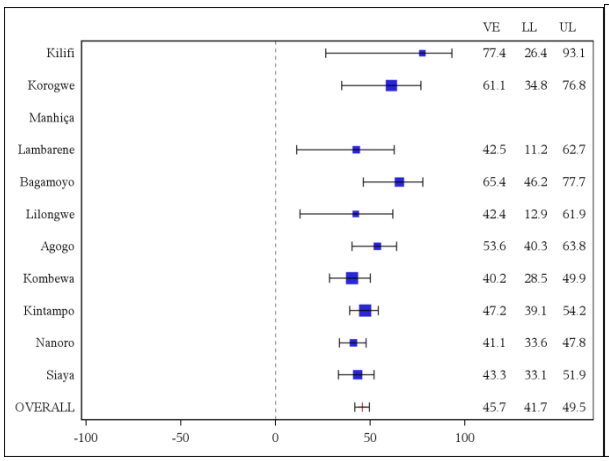
[1] It is important to note the limitation that the groups have different histories of malaria disease at the start of the time intervals after the first, so some prefer to term these estimates comparative incidence rather than vaccine efficacy. We have used vaccine efficacy throughout this document for consistency with terminology in the final Phase 3 publication.

groups in the last period. The estimates of incidence in the RTS,S-vaccinated group remains favourable over the study period, both among those receiving and not receiving a fourth dose (Table 4.1).

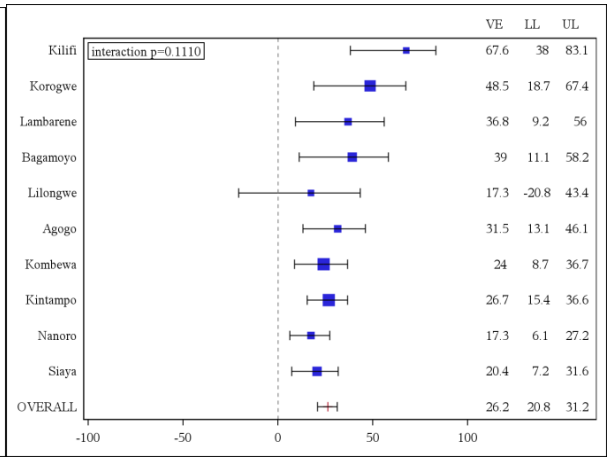
By trial site, vaccine efficacy estimates 18 months following the first three doses ranged from 40.2% (95%CI 28.5, 49.9) in Kombewa, a high transmission setting, to 77.4% (95%CI 26.4, 93.1) in Kilifi, a low transmission setting (Figure 4.4). Up to the end of the study, vaccine efficacy at each study site was higher among those who received a fourth dose, although the confidence intervals are wide. There were not markedly different estimates for vaccines efficacy by site. Still, in the 5-17 months group, the trend test (for higher VE as transmission decreases) was significant without and with the fourth dose (p=0.0095 and p=0.0157, respectively). At each time point the lower limit of the 95% confidence interval for the site-specific efficacy estimate was above 0, with one exception (Figure 4.4b). Vaccine efficacy declined similarly across transmission sites over time.

Of note, Nanoro was a strongly annual seasonal site (Figure 3.2). Trial participants in the 5-17 month age category were recruited to the trial more quickly than the infant group, and in the case of Nanoro, just after the transmission season. In the context of rapidly waning immunity, vaccine efficacy may not have optimally protected Nanoro participants and underestimated potential protection from vaccination.

a) FU: M2.5-20



b) FU: M2.5-SE, 3-dose schedule



c) FU: M2.5-SE, 4-dose schedule

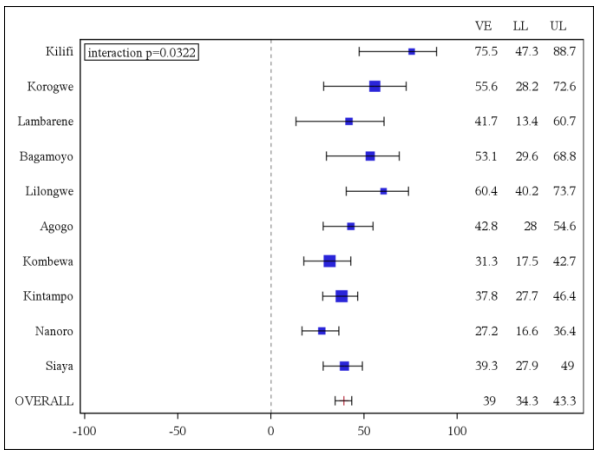


Figure 4.4 a-c Forest plots: Vaccine efficacy against all episodes of clinical malaria (primary case definition) (5-17 month age category) (ATP population). Sites are ordered based on incidence of clinical malaria (secondary case definition) measured in control infants 6-12 weeks of age at enrolment during 12 months of follow up. Provided by GSK on request.

Vaccine efficacy over 18 month follow-up after third dose of RTS,S was also analysed by age in months at first vaccination in the 5-17 month age category (Figure 4.5). No difference in vaccine efficacy by age at administration of the first dose was detected (trend test: p=0.1795), suggesting that vaccine efficacy does not improve with immune maturation in this age category.

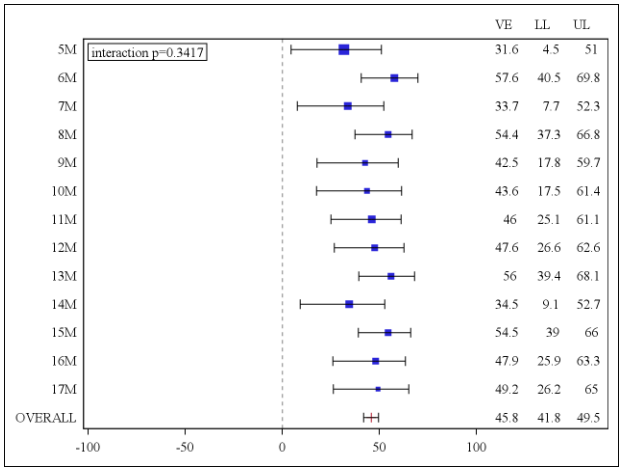


Figure 4.5: Vaccine efficacy against all episodes of clinical malaria by age in month at the time of first vaccination in the 5-17 month age category (primary case definition by age) (FU: M2.5-M20) (ATP population). Provided by GSK on request.

4.2.2 VE against all episodes of clinical malaria: 6-12 weeks age category

Vaccine efficacy against all episodes of clinical malaria 12 months following the first three doses was 32.9% (95%CI 26.3, 38.9) across all sites (Table 4.2). For the period 18 months, efficacy declined to 26.6% (95%CI 20.3, 32.4) and for the whole trial period to 18.2% (95%CI 11.4, 24.5) (median 38 months follow up post dose 3) amongst participants who did not receive a fourth dose of RTS,S. The addition of a fourth dose 18 months following the first three doses increased overall efficacy to 26.7% (95%CI 20.5, 32.4) from the first three doses to the trial end. The results did not substantially change with vaccine efficacy estimates based on secondary case definitions or with the ITT population.

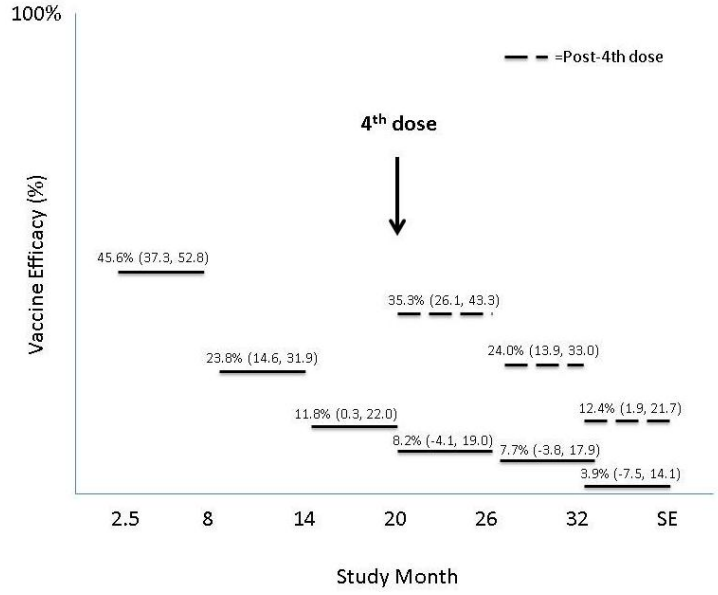
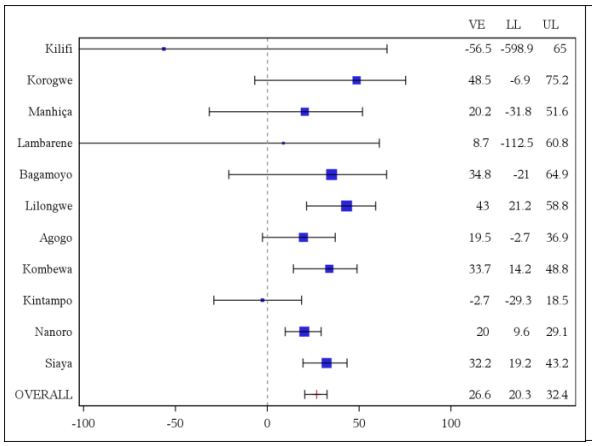


Figure 4.6: Vaccine efficacy stratified by time period in the 6-12 week age category in the Phase 3 trial (primary case definition, ATP population). Data provided by GSK on request.

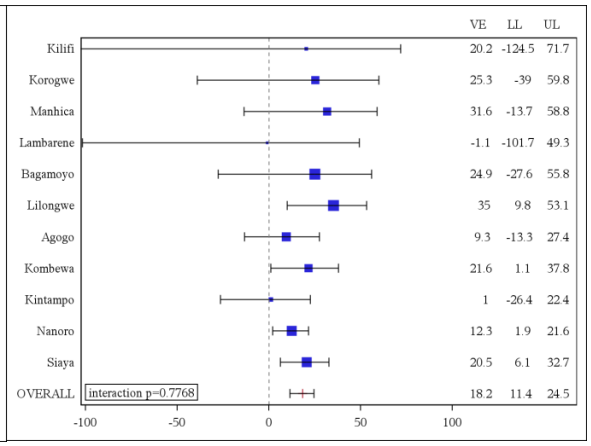
When vaccine efficacy was broken down by time interval (noting the limitation pointed out for the older age group above), the efficacy following three doses alone declined in successive six-month periods from 45.6% (95%CI 37.3, 52.8) in the first six months to 23.8% (95%CI 14.6, 31.9), 11.8% (95%CI 0.3, 22.0), 8.2% (-4.1, 19.0), 7.7% (95%CI -3.8, 17.9), and finally to 3.9% (95%CI -7.5, 14.1) (Figure 4.6). For the first six months that followed receipt of the fourth dose, vaccine efficacy was estimated

to be 35.3% (95%CI 26.1, 43.3), which then decreased to 24.0% (95%CI 13.9, 33.0) over the subsequent six months. From 12 months after the fourth dose to the trial end, efficacy was estimated at 12.4% (95%CI 1.9, 21.7). Administration of a fourth dose did not increase efficacy to the level obtained by the first three doses.

a) FU: M2.5-20



b) FU: M2.5-SE 3 dose schedule



c) FU: M2.5-SE 4 dose schedule

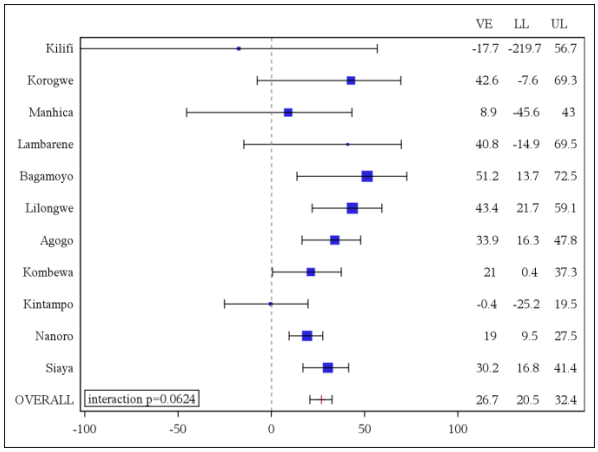


Figure 4.7 a-c Forest plots: Vaccine efficacy against all episodes of clinical malaria (primary case definition) (6-12 week age category) (ATP population). Sites are ordered based on incidence of clinical malaria (secondary case definition) measured in control infants 6-12 weeks of age at enrolment during 12 months of follow up. Provided by GSK on request.

There was not a clear correlation between vaccine efficacy in the 18 months following the vaccination by site and transmission intensity in the 6-12 week age group (Figure 4.7). A trend test of efficacy by site was not significant, without or with the fourth dose (p=0.4835 and p=0.6971, respectively).

4.3 Vaccine efficacy against severe malaria

4.3.1 VE against severe malaria: 5-17 months age category

Vaccine efficacy against all episodes of severe malaria in the first 12 months was 44.5% (95%CI 23.8, 59.6) (Table 4.1). Up to 18 months, the efficacy was estimated at 37.7% (95%CI 18.0, 52.6), and by the trial end (in the group without a fourth dose of RTS,S), the overall efficacy was estimated at -2.2% (95%CI -31.3, 20.4), suggesting that three doses alone had no effect on the overall incidence of

severe malaria, the apparent protective effect in the first 18 months being balanced by a rebound of cases in the period from 18 months to the end of the trial. Among trial participants who received a fourth dose, the vaccine efficacy against severe malaria up to the end of the trial was 31.5% (95%CI 9.3, 48.3).

When vaccine efficacy was analysed by time interval (again with the limitation noted above), efficacy against severe malaria was high in the first 6 months of follow up at 70.1% (95%CI 49.0, 82.5), but steadily declined to -47.9% (95%CI -134.6, 6.8) between 19-30 months after the first three doses were given, and to -74.2% (95%CI -220.0, 5.2) between 31 months and the end of the observation period (Table 4.4). Amongst participations who received a fourth dose of RTS,S at 18 months, efficacy against severe malaria was -6.0 (95%CI -75.2, 35.9) between 19-30 months after the first three doses, and to -22.7% (95%CI -137.9, 36.8) between 31 months and the end of the observation period. Given the positive efficacy over the full observation period in the group that received the fourth dose (31.5%, 95%CI 9.3, 48.3), there was an overall beneficial effect against severe malaria in those who received a fourth dose during the full observation period.

Study Month	Pooled RTS,S groups (R3C + R3R)	
M2.5-M8	70.1 (49.0, 82.5)	
M9-M14	20.5 (-17.8, 46.4)	
M15-M20	14.6 (-41.0, 48.2)	
Study Month	**3-dose schedule (R3C)**	**4-dose schedule (R3R)**
M21-M32	-47.9 (-134.6, 6.8)	-6.0 (-75.2, 35.9)
M33-SE	-74.2 (-220.0, 5.2)	-22.7 (-137.9, 36.8)
M2.5-SE	**-2.2** **(-31.3, 20.4)**	**31.5** **(9.3, 48.3)**

Table 4.4: Vaccine efficacy VE% (95%CI) against all episodes of severe malaria in 5-17 months age category by study months – primary case definition, ATP population. Provided by GSK on request. Case counts available in Appendix 3.

Many sites experienced too few cases to generate a reliable site-specific estimates for vaccine efficacy against severe malaria. In nearly all sites, even across the full study period, confidence intervals were wide and crossed zero (Figure 4.8). Given the small numbers it is difficult to draw any firm conclusions about variations in efficacy between sites.

a) M0-SE: 3 dose schedule **b) M0-SE: 4 dose schedule**

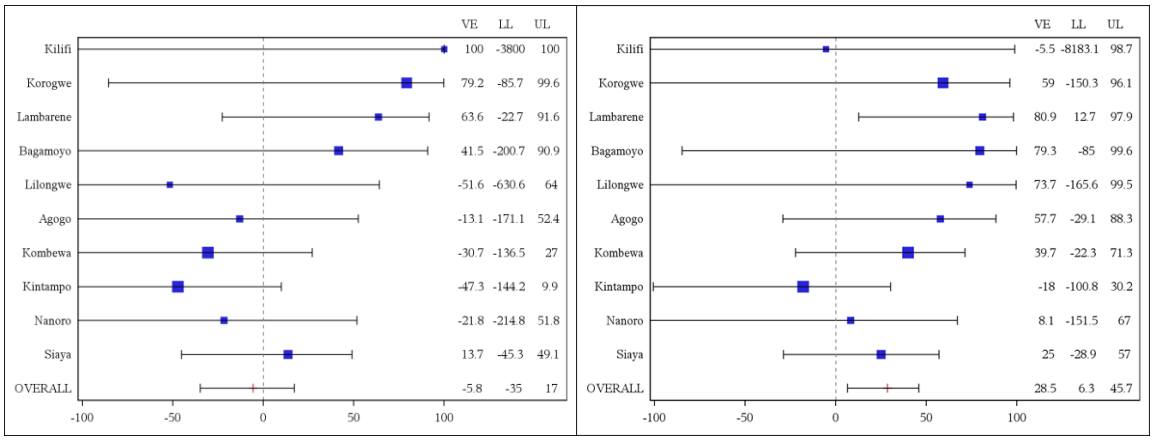


Figure 4.8 a-b Forest plots: Vaccine efficacy in 5-17 month age category against severe malaria by site (primary case definition) (ATP population). Sites are ordered based on incidence of clinical malaria (secondary case definition) measured in control infants 6-12 weeks of age at enrolment during 12 months of follow up. Provided by GSK on request.

Figure 4.2 shows the incidence of severe malaria among participants in the 5-17 month age category over the course of the trial. The difference between the RTS,S and control groups is evident at the beginning of the trial; however, by study month 25 (23 months after vaccination), the incidence of severe malaria in group that received three doses of RTS,S without a fourth dose is generally higher than in the control group. Across all treatment groups, the incidence of severe malaria decreases by study month to a low level by the end of the trial. There is an indication that the overall incidence of severe malaria is declining in all groups, suggesting that any late rebound beyond the period of follow-up in the participants who received a fourth dose may not cancel out the overall protective effect in this group.

Importantly, a similar shift in cases of severe malaria towards older children was seen in the 6-12 week age group, but with a shorter timeframe, consistent with the overall lower efficacy in this age group. Thus the period of negative vaccine efficacy occurs at the 12-18 month time period following the third dose, and further follow-up shows no excess of severe malaria cases thereafter (see Table 4.7). If the same pattern followed in the 5-17 month age group, one would expect to see no excess of cases beyond the end of the trial, with low incidence of severe malaria regardless of randomization group.

From the time when the fourth dose was administered to the trial end, there were 103 cases of severe malaria in the RTS,S group that received a control vaccine at 18 months (R3C), compared to 76 cases in the RTS,S group that did receive a fourth dose of RTS,S (R3R) and 76 cases in the control group (C3C). The majority of cases classified as severe malaria, and most of the excess cases, were associated with other severe disease markers (prostration, respiratory distress, seizures, hypoglycaemia, etc.) rather than cerebral malaria or anaemia. The case fatality rate of these “other” cases is low. Of those severe cases who received RTS,S (R3R and R3C), there appeared to be a tendency for severe malaria to manifest as cerebral malaria (Table 4.5), although the absolute numbers of cerebral malaria cases remain low. The case fatality rate in the trial was lower than usually seen outside a trial setting. Over the first 20 months of the trial, 6 cases who received RTS,S died, and 2 cases in the control group died (2:1 randomization). From month 21 to the study end, six

cases died in the R3C group, three cases died in the R3R group, and two died in the C3C group. A review of the cerebral malaria cases by site showed a distribution consistent with the transmission settings of each site (Table 4.6).

Table 4.5: Cases of severe malaria disease (secondary case definition 1) classified by syndrome, group and time period including fatal cases by syndrome (ITT population; 5-17 month age category). Provided by GSK on request.

Time Period	Syndrome	RTS,S group (R3C + R3R) N=5948		Control group (C3C) N=2974	
		N	Died	N	Died
M0-M20	All Cases	205	6	158	2
	Cerebral	16	3	5	1
	Cerebral + Anaemia	6	1	1	0
	Anaemia	25	0	29	1
	Other	157	2	123	0
	Missing	1	0	0	0

Time period	Syndrome	3-dose schedule (R3C) N=2719		4-dose schedule (R3R) N=2681		Control (C3C) N=2702	
		N	Died	N	Died	N	Died
M21-SE	All Cases	103	6	76	3	76	2
	Cerebral	9	4	11	2	2	0
	Cerebral + Anaemia	0	0	1	0	2	1
	Anaemia	18	1	11	0	17	0
	Other	75	1	53	1	54	1

All cases: Secondary case definition 1 (more than 5000 parasites and at least 1 marker, including comorbidities)
Cerebral: more than 5000 parasites and BCS <= 2 and Hb >= 5 g/dl
Anaemia: more than 5000 parasites and BCS > 2 and Hb < 5 g/dl
Cerebral+Anaemia: 5000 parasites and BCS <= 2 and Hb < 5 g/dl
Other: 5000 parasites and other severe disease marker (prostration, respiratory distress, seizures, hypoglycemia < 2.2 mmol/L, acidosis BE ≤-10.0 mmol/L, lactate ≥ 5.0 mmol/L) excluding BCS and Hb

Table 4.6: Cerebral malaria cases in the 5-17 month age category by site. Provided by GSK on request.

Site	Number of subjects by site 5-17 months	Number of cases of cerebral malaria 5-17 months
Siaya	799	9
Kintampo	1002	14
Nanoro	600	8
Agogo	600	8
Manhica	1002	3
Lambarene	704	3
Kombewa	1000	4
Lilongwe	800	2
Bagamoyo	903	2
Korogwe	912	0
Kilifi	600	0
Total	**8922**	**53**

4.3.2 VE against severe malaria 6-12 weeks age category

Vaccine efficacy against severe malaria in the first 12 months was 38.5% (95%CI 7.8, 59.0) (Table 4.2). At 18 months, the efficacy was estimated at 17.4% (95%CI -16.2, 41.3), and by the trial end (in the group without a fourth dose of RTS,S), the efficacy was estimated at 16.0% (95%CI -14.5, 38.4). Among 6-12 week trial participants who received a fourth dose, the vaccine efficacy to the end of the trial was 20.5% (95%CI -9.8, 42.5).

When this was broken down by time interval, efficacy against severe malaria was 53.7% (95%CI 18.7, 73.6) in the first 6 months, after which the confidence intervals are wide and cross zero, although the point estimate is negative for the 12-18 month follow-up period, with no excess of severe malaria cases in those vaccinated beyond this initial period of rebound. Efficacy against severe malaria was 4.7% (-52.8, 40.6) between 19-30 months after the 3 doses, and 7.3% (95%CI -113.0, 59.9) between 31 months and the end of the observation period without a fourth dose (Table 4.7).

Study Month	Pooled RTS,S groups (R3C + R3R)	
M2.5-M8	53.7 (18.7, 73.6)	
M9-M14	18.2 (-43.8, 53.5)	
M15-M20	-38.9 (-143.2, 20.6)	
Study Month	**3-dose schedule (R3C)**	**4-dose schedule (R3R)**
M21-M32	4.7 (-52.8, 40.6)	37.7 (-4.8, 63.0)
M33-SE	7.3 (-113.0, 59.9)	13.8 (-91.6, 61.2)
M2.5-SE	**16.0 (-14.5, 38.4)**	**20.5 (-9.8, 42.5)**

Table 4.7: Vaccine efficacy against all episodes of severe malaria in 6-12 week age category by study months – primary case definition, ATP population. Provided by GSK on request. Case counts available in Appendix 3.

Stratification by site in this age group shows a wide variation in point-estimates and very wide confidence intervals due to the rarity of the outcome (Figure 4.9).

a) M2.5-SE: 3 doses of RTS,S **b) M2.5-SE: 4 doses of RTS,S**

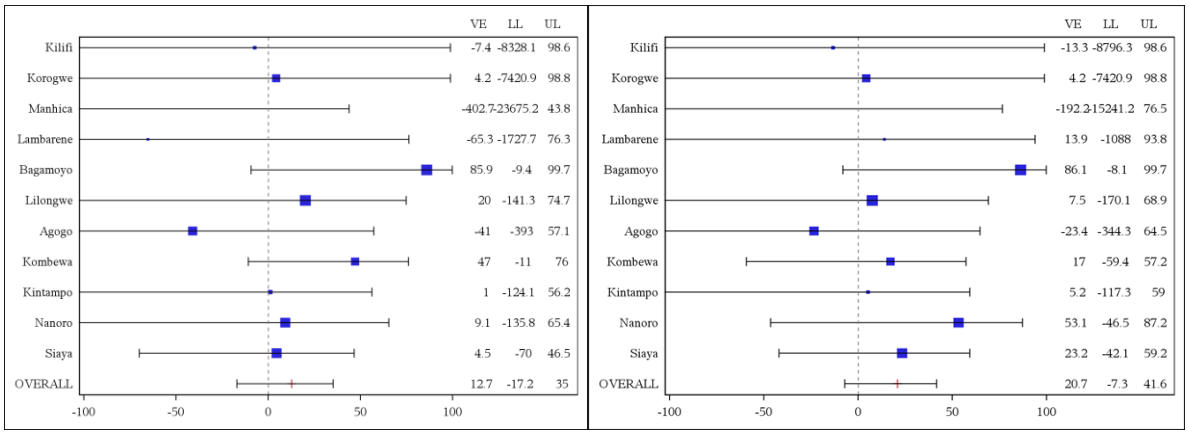


Figure 4.9: Vaccine efficacy in 6-12 week category against severe malaria by site (primary case definition) (ATP population). Sites are ordered based on incidence of clinical malaria (secondary case definition) measured in control infants 6-12 weeks of age at enrolment during 12 months of follow up. Provided by GSK on request.

Cases of severe malaria were also broken down by syndrome for the 6-12 week age category (Table 4.8). In contrast to the 5-17 month category, there was no imbalance between the RTS,S group and the control group in cerebral malaria cases.

Table 4.8: Cases of severe malaria disease (secondary case definition 1) classified by syndrome, group and time period including fatal cases by syndrome (ITT population; 6-12 week age category). Provided by GSK on request.

Time Period	Syndrome	RTS,S group (R3C + R3R) N=4358		Control group (C3C) N=2179	
		N	Died	N	Died
M0-M20	All Cases	148	1	86	2
	Cerebral	2	0	3	0
	Cerebral + Anaemia	3	0	1	0
	Anaemia	30	0	17	0
	Other	111	1	65	2
	Missing	2	0	0	0

Time period	Syndrome	3-dose schedule (R3C) N=1996		4-dose schedule (R3R) N=1966		Control (C3C) N=1976	
		N	Died	N	Died	N	Died
M21-SE	All Cases	63	2	53	3	68	0
	Cerebral	4	1	4	2	2	0
	Cerebral + Anaemia	0	0	0	0	1	0
	Anaemia	15	0	15	0	19	0
	Other	42	0	34	1	45	0
	Missing	2	1	0	0	1	0

All cases: Secondary case definition 1 (more than 5000 parasites and at least 1 marker, including comorbidities)
Cerebral: more than 5000 parasites and BCS <= 2 and Hb >= 5 g/dl
Anaemia: more than 5000 parasites and BCS > 2 and Hb < 5 g/dl
Cerebral+Anaemia: 5000 parasites and BCS <= 2 and Hb < 5 g/dl
Other: 5000 parasites and other severe disease marker (prostration, respiratory distress, seizures, hypoglycemia < 2.2 mmol/L, acidosis BE ≤-10.0 mmol/L, lactate ≥ 5.0 mmol/L) excluding BCS and Hb

4.4 VE against malaria hospitalization and mortality

Table 4.9: Vaccine efficacy (95%CI) against additional outcomes (primary case definitions or case definition 1; ATP population). Provided by GSK on request.

Outcome	5-17 months			6-12 weeks		
	M2.5-20 Pooled RTS,S (R3R + R3R)	M2.5-SE 3-dose schedule (R3C)	M2.5-SE 4-dose schedule (R3R)	M2.5-20 Pooled RTS,S (R3R + R3R)	M2.5-SE 3-dose schedule (R3C)	M2.5-SE 4-dose schedule (R3R)
Malaria hospitalization	41.7 (29.4-51.8)	12.1 (-5.0-26.4)	37.2 (23.6-48.5)	17.8 (-6.3-36.2)	13.2 (-9.2-31.1)	27.1 (7.1-42.9)
Incident Severe anaemia	56.6 (21.3-76.2)	20.6 (-32.7-52.9)	61.2 (26.5-80.6)	3.0 (-100-50.9)	12.8 (-50.9-49.9)	31.5 (-23.1-62.6)
All-cause hospitalization	19.1 (8.7-28.2)	8.8 (-2.9-19.3)	14.9 (3.6-24.8)	6.5 (-6.2-17.5)	4.8 (-8.3-16.4)	7.0 (-6.0-18.4)
All-cause hospitalization excluding malaria	6.0 (-9.1-18.8)	6.6 (-8.5-19.6)	3.2 (-12.4-16.5)	2.0 (-12.9-14.8)	1.8 (-13.8-15.2)	-0.3 (-16.2-13.4)
All-cause mortality	7.3 (-63.8-46.2)	-1.3 (-79.5-42.8)	-17.8 (-105-31.9)	-9.0 (-84.9-43.0)	-21.5 (-108-28.5)	-15.6 (-99.2-32.6)
Bacteraemia	15.8 (-26.0-43.2)	22.3 (-16.0-48.3)	12.8 (-28.9-41.1)	-21.9 (-101-23.9)	-19.6 (-85.8-22.6)	-8.5 (-70.3-30.7)
Pneumonia	6.4 (-28.0-31.0)	21.2 (-10.9-44.2)	-3.9 (-43.0-24.5)	10.5 (-17.9-31.7)	16.4 (-11.4-37.4)	11.0 (-18.2-33.0)

4.4.1 VE against malaria-related hospitalization, mortality and severe anaemia: 5-17 months age category

In the 5-17 month age category, vaccine efficacy against malaria-related hospitalization (defined as a medical hospitalization with confirmed *P. falciparum* >5000 parasites/µL) was 41.7% (95%CI 29.4, 51.8) up to study month 20 (Table 4.9). Among participants who did not receive the fourth dose (R3C), efficacy against malaria-related hospitalization was 12.1% (95%CI -5.0, 26.4) by the trial end. Among participants who did receive the fourth dose (R3R), vaccine efficacy against malaria-related hospitalization was 37.2% (95%CI 23.6, 48.5) during the full observation period.

Vaccine efficacy against malaria-related mortality based on the primary case definition (defined as a case of severe malaria meeting the primary case definition of severe malaria with a fatal outcome) could generally not be assessed due to the lack of cases. During the first 20 months of the study,

there were 12 malaria-related deaths in the RTS,S group and 7 malaria-related deaths in the control group (2:1 randomization) (Table 4.10). From 21 months to the study end, there were 11 malaria-related deaths in the RTS,S group that did not receive a fourth dose (R3C), 7 malaria-related deaths in the group that did receive a fourth dose (R3R), and 5 malaria-related deaths in the control group.

During the full study period, vaccine efficacy against incident severe anaemia (defined as 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) was 20.6% (95%CI -32.7, 52.9) in the group that did not receive a fourth dose (R3C), and it was 61.2% (95%CI 26.5, 80.6) in the group that did receive a fourth dose (R3R).

4.4.2 VE against malaria-related hospitalization, mortality and severe anaemia: 6-12 weeks age category

In the 6-12 week age category, vaccine efficacy against malaria-related hospitalization was 17.8% (95%CI -6.3, 36.2) up to study month 20 (Table 4.9). Among participants who did not receive the fourth dose (R3C), efficacy was against malaria-related hospitalization was 13.2% (95%CI -9.2, 31.1) to the trial end. Among participants who did receive the fourth dose (R3R), vaccine efficacy against malaria-related hospitalization was 27.1% (95%CI 7.1, 42.9) during the full observation period.

Table 4.10: Number of fatalities due to malaria or all-causes by treatment group and time period (ITT population; Fatal malaria based on ICD10 code (B50, B53, B54) case review). Provided by GSK on request.

5-17 Months age category		Pooled RTS,S (R3R + R3R) (N=5948)	3-dose schedule (R3C) (N=2719)	4-dose schedule (R3R) (N=2681)	Control (C3C) (N=2702)
Fatal malaria cases (N)	M0-M20	12	-	-	7
	M21-SE	-	11	7	5
All-cause mortality (N)	M0-M20	74	-	-	33
	M21-SE	-	23	15	13
6-12 Week age category		**Pooled RTS,S (R3R + R3R) (N=4385)**	**3-dose schedule (R3C) (N=2178)**	**4-dose schedule (R3R) (N=2180)**	**Control (C3C) (N=2179)**
Fatal malaria cases (N)	M0-M20	9	-	-	4
	M21-SE	-	6	5	2
All-cause mortality (N)	M0-M20	83	-	-	34
	M21-SE	-	11	11	8

Vaccine efficacy against malaria-related mortality based on the primary case definition could generally not be assessed due to the lack of cases. During the first 20 months of the study, there were 9 malaria-related deaths in the RTS,S group and 4 malaria-related deaths in the control group (2:1 randomization) (Table 4.10). From 21 months to the study end, there were 6 malaria-related deaths in the RTS,S group that did not receive a fourth dose (R3C), 5 malaria-related deaths in the group that did receive a fourth dose (R3R), and 2 malaria-related deaths in the control group.

During the full study period, vaccine efficacy against incident severe anaemia was 12.8% (95%CI -50.9, 49.9) in the group that did not receive a fourth dose (R3C), and it was 31.5% (95%CI -23.1, 62.6) in the group that did receive a fourth dose (R3R).

4.5 VE against other outcomes

4.5.1 VE against other outcomes: 5-17 months age category

Vaccine efficacy was assessed also against all-cause hospitalization, all-cause mortality, bacteraemia, and pneumonia (Table 4.9). Among these, the only significant protection demonstrated was in the 5-17 month category against all-cause hospitalization (including malaria-related hospitalizations) in the first 18 months after third vaccination (R3C + R3R) and in the full study period among those who received a fourth dose (R3R). The efficacy estimates were 19.1% (95%CI 8.7, 28.2) and 14.9% (95%CI 3.6, 24.8), respectively. When malaria was excluded as a cause of hospitalization, the vaccine efficacy estimates were no longer significant.

During the first 20 months of the study (M0-M20), there were 74 deaths from any cause in the RTS,S groups and 33 deaths in the control group (2:1 randomization) (Table 4.10). From 21 months to the study end (M21-SE), there were 23 deaths in the RTS,S group that did not receive a fourth dose (R3C), 15 deaths in the group that did receive a fourth dose (R3R), and 13 deaths in the control group. The efficacy against all-cause mortality (defined as a fatality of any cause that occurs in the community or in hospital) up to study month 20 was 7.3% (95%CI -63.8, 46.2) in 5-17 month old participants. Across the entire study period, the vaccine efficacy against all-cause mortality was –1.3% (95%CI -79.5, 42.8) in those without a fourth dose (R3C), and -17.8% (95%CI -105, 31.9) among those who did receive a fourth dose of RTS,S (R3R). Mortality overall was low in the follow-up period across all groups (1.8%).

4.5.2 VE against other outcomes: 6-12 weeks age category

In the 6-12 weeks age category, vaccine efficacy was not significant in any group for the outcomes reviewed: all-cause hospitalization, all-cause mortality, bacteraemia, and pneumonia (Table 4.9)

During the first 20 months of the study (M0-M20), there were 83 deaths from any cause in the RTS,S group and 34 deaths in the control group (2:1 randomization) (Table 4.10). From 21 months to the study end (M21-SE), there were 11 deaths in the RTS,S group that did not receive a fourth dose (R3C), 11 deaths in the group that did receive a fourth dose (R3R), and 8 deaths in the control group. The efficacy against all-cause mortality up to study month 20 was -9.0% (95%CI -84.9, 43.0) in 6-12 week old participants. Across the entire study period, vaccine efficacy against all-cause mortality was -21.5% (95%CI -108, 28.5) in those without a fourth dose (R3C), and -15.6% (95%CI -99.2, 32.6) among those who did receive a fourth dose (R3R). Mortality was also low (2.3%) in young infants across all groups.

The efficacy against all-cause hospitalizations was 6.5% at study month 20 (95%CI –6.2, 17.5). By the trial end, vaccine efficacy was estimated at 4.8% (95%CI -8.3, 16.4) in the group that did not receive a fourth dose (R3C) and 7.0% (95%CI -6.0, 18.4) in the group that did receive a fourth dose (R3R).

4.5.3 Mortality among participants in the RTS,S clinical trial

As remarked above, this trial did not identify an effect of vaccination on mortality. There were relatively few deaths in the trial (Table 4.10), far less that would have been expected in the absence of the trial. A case-control analysis at the KEMRI/CDC RTS,S trial site (also a DSS site) in Kisumu Kenya identified a 70% reduction in mortality among children who participated in the control arm of the trial compared to those who live in the DSS catchment area but did not participate in the trial[27]. This trial was not powered to detect a possible reduction in mortality due to vaccination in either the 5-17 month age category or 6-12 week age category, and it remains an open question as to whether the vaccine will produce a mortality reduction if deployed in populations in which the standard of care may be less than experienced by children in the Phase 3 trial.

4.6 Summary of VE profile of RTS,S/AS01 & RTS,S/AS02 in Phase 2 trials

Table 4.11 summarises results from Phase 2 trials. All paediatric trials show significant protection against clinical malaria.

Table 4.11: Overview of vaccine efficacy estimates from Phase 2 trials of AS01- and AS02-containing RTS,S vaccine (adapted from Bejon et al 2013)[28].

Country	Subjects (n)	Active vaccine(s)	Control vaccine	Surveillance	Median age at enrolment (IQR)	Local parasite prevalence (%)	Duration of follow up post-dose 3	Vaccine Efficacy (95%CI)
Gambia	250	RTS,S/AS02	Rabies	ACDi, weekly blood films	24 years (19-34)	70%	15 weeks	34 % (8, 53)
Kenya	250	RTS,S/AS02 RTS,S/AS01	Rabies	ACDi, weekly blood films	25 years (21-29)	60%	14 weeks	30% (-15, 57)
Mozambique	411	RTS,S/AS02	HepB or PCV/Hib	ACDi, blood films every 3 weeks	36 months (24-45)	70%	6 months	45% (31, 56)
Mozambique	214	RTS,S/AS02	HepB	ACDi, blood films every 2 weeks	1.8 months (1.8-2.1)	45%	3 months	66% (43, 80)
Tanzania	340	RTS,S/AS02	HepB	ACDi, blood films every 2 weeks	1.9 months (1.8-2)	30%	6 months	65% (21, 85)
Kenya	447	RTS,S/AS01	Rabies	ACDc, weekly visits	11 months (8-14)	35%	Variable (mean of 7.9 months)	53% (28, 69)
Tanzania	447				12 months (9-15)	15%		
Mozambique	1589	RTS,S/AS02	HepB or PCV/Hib	PCD	35 months (24-48)	40%	6 months	30% (11, 45)
Tanzania	209	RTS,S/AS01	None	PCD	1.8 months (1.7-1.9)	30%	16.5 months	53% (26, 70)
Gabon	215				1.5 months (1.4-1.7)	5%		
Ghana	81				1.6 months (1.5-1.8)	80%		

ACDi=active case detection for infection. ACDc=active case detection for clinical malaria. PCD=passive case detection for clinical malaria. Active case detection includes a passive component.

5. RTS,S Immunogenicity

5.1 Theoretical mechanism of action

It has been established that RTS,S/AS reduces the rate of acquisition of new blood stage infections[29], reduces the initial inoculum of each blood stage infection[30] and reduces the multiplicity of infections in vaccinees[31]. This might result from the induction of CS-specific antibodies and/or $CD4^+$ T cells and to date there are no accepted correlates of protection for RTS,S/AS[32].

The available evidence about the protective mechanism of RTS,S/AS, however, supports a critical role for IgG against the CS repeat sequence in the protection seen against infection, whether in multiple clinical challenge trials in USA, adult or paediatric field trials in different age groups and across the distinct transmission settings of The Gambia, Kenya, Tanzania and Mozambique[7]. When a mosquito probes for a blood meal, sporozoites are deposited intradermally and migrate for several hours before entering skin microvasculature or entering lymphatics[33, 34], although some sporozoites may perhaps entering directly into vessels during mosquito probing. Anti-CS antibodies have been shown to reduce the numbers of sporozoites that enter skin blood vessels to begin the journey to the liver[35]. No anti-CS antibody threshold level has been found as indicative of full protection against infection: the data are consistent with a dose response such that at higher IgG concentrations a reduced risk of infection is seen. Importantly, antibody titres after the fourth dose do not reach levels seen after the first three doses, which is consistent with efficacy also not being as high. The reasons for this are not fully understood. One hypothesis is that high titre hepatitis B antibodies induced by first three doses would interfere with subsequent induction of anti-CS immunogenicity. A more likely hypothesis, supported by the lower anti-CS titers elicited in malaria-immune than naïve adults[14], is that increasing exposure to CS – whether through repeated malaria infection or vaccination - leads to B cell hyporesponsiveness. This phenomenon, first described for meningococcal and pneumococcal polysaccharide vaccines[36], reflects the recruitment and differentiation of fewer antigen-specific B cells into successive responses, the B cell reservoir being exhausted by repeat and/or high-dose antigen exposure. This has two implications: 1) the booster dose is a fourth dose; 2) the capacity of subsequent doses to “reactivate” immunity and protection is unknown and difficult to predict.

Cell-mediated immunity (CMI) indicators were used as a down-selection criterion for adjuvant choice in the RTS,S development programme[37]. Both CS-specific γ-interferon secreting $CD4^+$ T cell responses (as enumerated by *ex vivo* ELISPOT) and multifunctional CS-specific $CD4^+$ T cells (defined as expressing two or more of γ-interferon, TNF, IL-2 and CD40 ligand using an intracellular cytokine staining assay) were greater in protected than in unprotected vaccinees in an RTS,S clinical challenge trial[14]. Multifunctional $CD4^+$ T cell responses were reported not to be correlated with anti-NANP IgG responses. Some data on CMI responses to RTS,S is available in African children[38], although none from the pivotal Phase 3 trial. Most RTS,S studies performing CMI studies have reported an absence of substantial CS-specific $CD8^+$ T cell responses[14, 39]. Weak CS-specific $CD8^+$ T cell responses were reported in a trial, with a highly sensitive ELISPOT assay performed on cultured cells[40]. $CD8^+$ T cells are thus not thought to be an important mediator of protection for RTS,S/AS01.

Prior to the pivotal Phase 3 study, there was a consistently reported association between IgG that bind CS and protection from infection, but not from disease. This is consistent with the pre-erythrocytic biological target of the vaccine. It is possible that complete protection occurs in some volunteers, but in high transmission settings most vaccinees do eventually develop malaria, suggesting that the proportion completely protected is, at most, small. This needs to be taken into account in interpreting associations of immune responses and efficacy, as partial protection from infection might be expected in most individuals. This also implies that vaccinated individuals, during the initial period when protected against malaria, also experience less exposure to blood-stage parasites and therefore may have a deferred development of naturally acquired immunity, which may render them later on more susceptible to adverse effects of malaria infection as vaccine efficacy wanes than persons who have not been vaccinated.

5.2 Summary of immunogenicity of RTS,S/AS in Phase 2 and Phase 3 studies, other than the Pivotal Phase 3 study

In the paediatric population, after 3 doses of RTS,S/AS01 vaccine given according to the 0, 1, 2-month schedule, over 98% of subjects were seropositive for anti-CS antibody response. Seropositivity was defined as 0.5 EU/ml. Immunogenicity tends to increase with decreasing age from adulthood to a peak at median age of 11-12 months (Table 5.1). From the age of 11-12 months, a decrease in immunogenicity with age de-escalation to infants vaccinated at 1-2 months of age is seen.

Table 5.1: Peak anti-CSP titre by Phase 2 clinical trial site[41]

Site	Participants (RTS,S)	Active vaccine	Median age (IQR)	Parasite prevalence[a]	Schedule	Peak anti-CSP titre (95% range)
Gambia [12]	250 (136)	RTS,S/AS02A	24 (19 to 34) years	70%	0,1,5,14 months	25 (13 to 43) µg/mL
Kisumu, Kenya [13]	250 (159)	RTS,S/AS02A and RTS,S/AS01B	25 (21 to 29) years	60%	0,1,2 months	34 (2 to 210) EU/mL
Manhica, Mozambique (cohort 1) [7,14]	1,589 (768)	RTS,S/AS02A	35 (24 to 48) months	40%	0,1,2 months	191 (9 to 916) EU/mL
Ilha Josina, Mozambique (cohort 2) [7,14]	411 (196)	RTS,S/AS02A	36 (24 to 45) months	45%	0,1,2 months	266 (16 to 1,390) EU/mL
Kilifi, Kenya [6,15]	447 (209)	RTS,S/AS01E	11 (8 to 14) months	35%	0,1,2 months	580 (104 to 1,922) EU/mL
Korogwe, Tanzania [6]	447 (224)	RTS,S/AS01E	12 (9 to 15) months	15%	0,1,2 months	493 (138 to 1,768) EU/mL
Kintampo, Ghana [10]	180 (180)	RTS,S/AS02D and RTS,S/AS01E	11 (8 to 14) months	80%	0,1,2 and 0,1,7 months	465 (73 to 2,632)[b] EU/mL
Kumasi, Ghana [10]	270 (270)	RTS,S/AS02D and RTS,S/AS01E	11 (7 to 13) months	35%	0,1,2 and 0,1,7 months	460 (84 to 1,785)[b] EU/mL
Lambaréné, Gabon [9]	180 (180)	RTS,S/AS02D and RTS,S/AS01E	38 (31 to 48) months	5%	0,1,2 months	198 (32 to 888) EU/mL
Bagamoyo, Tanzania [8]	209 (136)	RTS,S/AS01E	1.8 (1.7 to 1.9) months	30%	0,1,2 and 0,1,7 months[c]	167 (14 to 934)[b] EU/mL
Lambaréné, Gabon [8]	215 (139)	RTS,S/AS01E	1.5 (1.4 to 1.7) months	5%	0,1,2 and 0,1,7 months[c]	337 (97 to 1,836)[b]EU/mL
Kintampo, Ghana [8]	81 (52)	RTS,S/AS01E	1.6 (1.5 to 1.8) months	80%	0,1,2 and 0,1,7 months[c]	70 (11 to 455)[b] EU/mL
Mozambique infants [16]	214 (98)	RTS,S/AS02D	1.8 (1.8 to 2.1) months	45%	0,1,2 months	211 (6 to 1,008) EU/mL
Bagamoyo, Tanzania [11]	340 (157)	RTS,S/AS02D	1.9 (1.8 to 2) months	30%	0,1,2 months[c]	87 (1 to 572)[b] EU/mL

For participants receiving at least one dose of RTS,S the peak anti-CSP antibody titre following vaccination is presented as the median and 95% range within the cohort at each trial site. [a]Age-corrected parasite prevalence in 2- to 10-year olds taken from Malaria Atlas Project [17]; [b]indicates peak anti-CSP antibody titre in the cohort vaccinated through a 0, 1, 2 month schedule; [c]indicates co-administration with the EPI vaccines (diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenza* type b). CSP, circumsporozoite protein; EPI, expanded programme on immunization; EU, ELISA units; IQR, interquartile range.

Table 5.1 shows peak anti-CS responses, generally measured 4 weeks after the final dose of RTS,S/AS01. The anti-CS antibody GMCs one month after the third dose tended to be higher in the

malaria-naïve adults (160.3 EU/ml in US adults, RTS,S/AS01 group) than in adults living in malaria-endemic areas (see first 2 rows in the table). In the first Phase 2b field efficacy trial, which involved 306 Gambian adults, 34% efficacy was reported against the incidence rate of first blood stage infections over a 15-week period[42]. In this study a linear relationship was found between IgG concentration post dose 3 and protection from blood stage infection, such that the odds ratio for a ten-fold increase in IgG concentration and infection with malaria was 0.21 (p = 0.023). After correction for age and pre-vaccination titre the odds ratio was 0.27 (p = 0.07).

The largest Phase 2b field efficacy trial of RTS,S/AS02 to date reported data on 2,022 Mozambican children, first vaccinated aged 1-4 years, and an association was found between anti-NANP IgG concentration and efficacy against malaria infection[43, 44]. A similar association was reported in a trial in infants in Mozambique[45]. In contrast, in paediatric trials there has generally been a lack of association between the anti-NANP IgG concentration and protection against clinical disease[29, 46].

The kinetics of the antibody response over time are shown in the Figure 5.1, from several Phase 2 studies in young children.

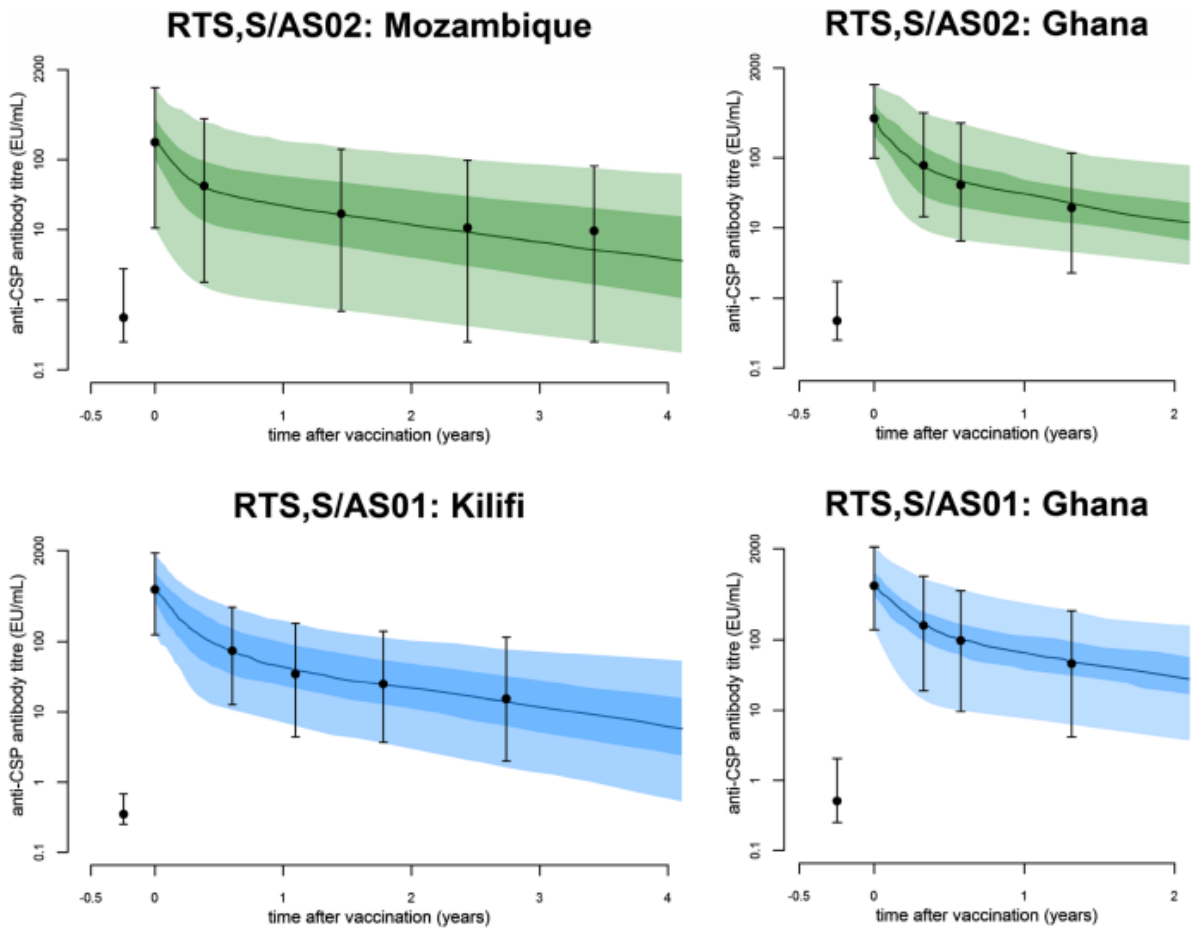


Figure 5.1: Decay of IgG titres from Phase 2 trials of RTS,S/AS02 and RTS,S/AS01[41].

Figure 5.1 highlights the biphasic decay of IgG titres, with a steeper decline in the six months following vaccination and a slower decline thereafter.

5.3 Summary of immunogenicity findings in the RTS,S/AS01 Phase 3 trial

RTS,S/AS01 was immunogenic in both age groups. There were very few non-responders to RTS,S. Anti-CS antibody geometric mean titres (GMTs) were highest at the measurement 1 month post-vaccination and did not return to the original level with a fourth dose (Figure 5.2). The absolute GMT value was higher in the 5-17 month age group compared to the 6-12 week age group at each time point following vaccination, as previously seen in Phase 2 studies. There was site-to-site variation in GMTs (Figures 5.4 and 5.5) and the reasons for this are not understood. Lot-to-lot consistency of immunogenicity has been demonstrated comparing three lots of vaccine formulated from commercial scale bulk material. These lots were shown to be at least as immunogenic (non-inferiority demonstrated for both anti-CS and anti-HBs immune response) as the vaccine lots used in the pivotal Phase 3 trial.

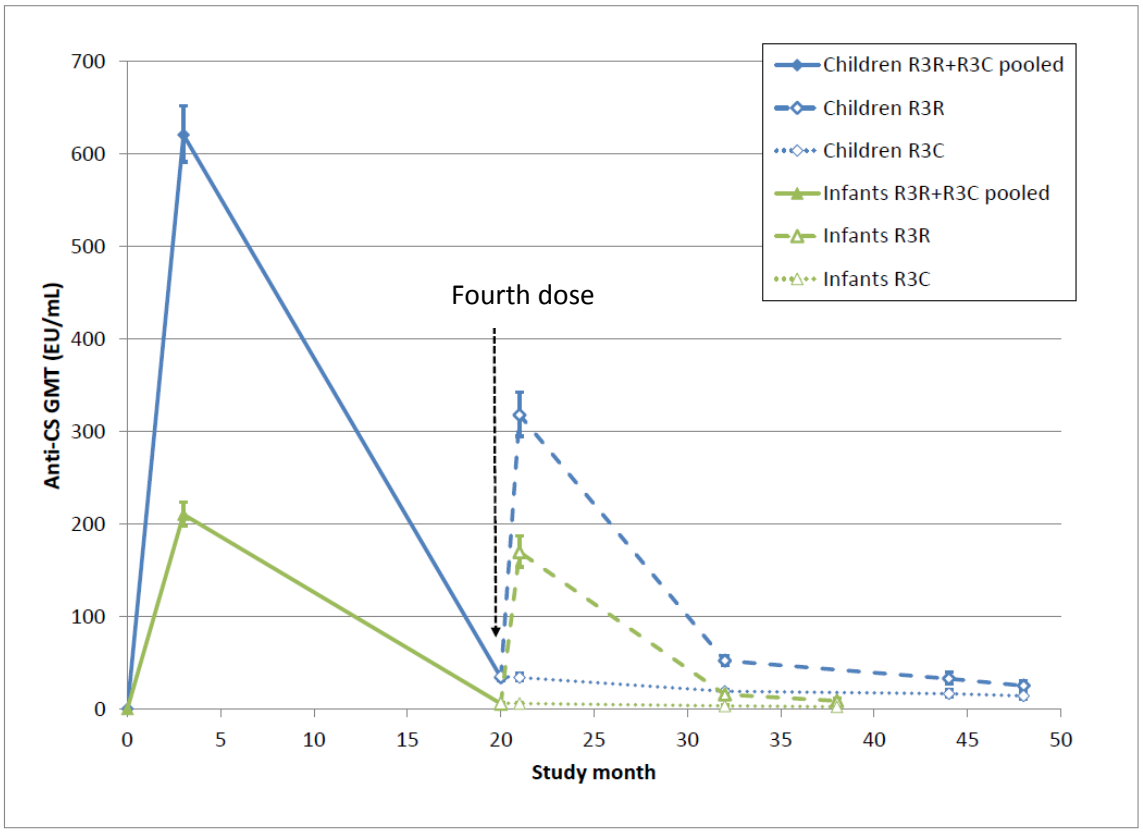
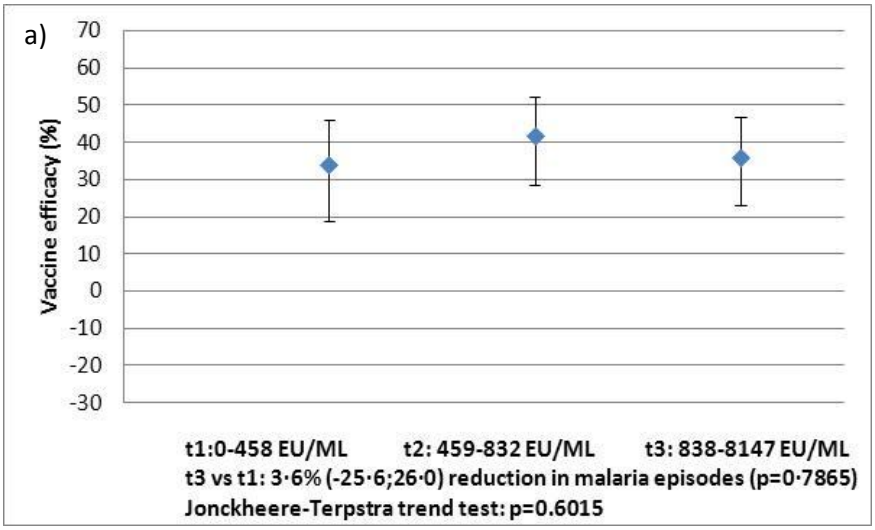


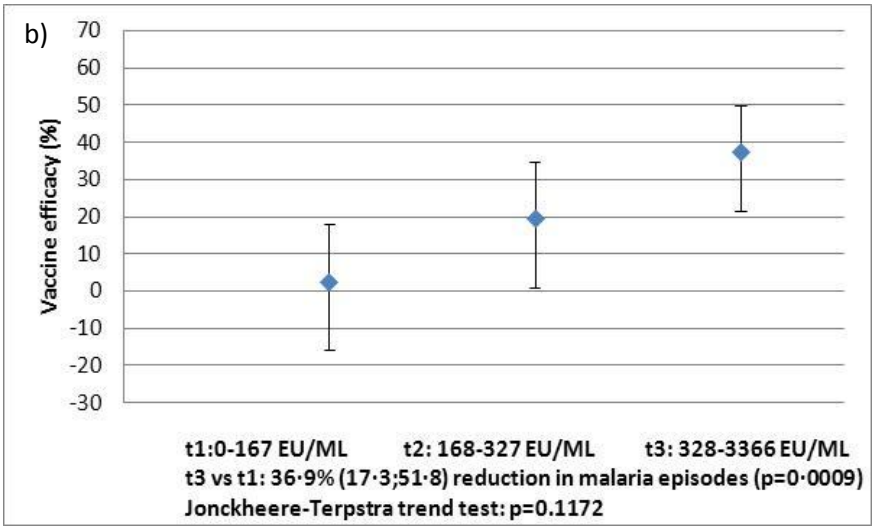
Figure 5.2: Anti-CS geometric mean titres in 5-17 month age category (labelled as "children") and 6-12 week old age category ("infants") in pivotal Phase 3 trial (per-protocol population for immunogenicity). Provided by GSK.

In order to interpret the immunogenicity data from the Phase 3 trial, it is necessary to consider the differences in pre-existing immunity between those in the 6-12 week and the 5-17 month age categories. The 6-12 week olds would have had variable quantities of pre-existing maternally acquired passive anti-CS IgG that may have interfered with vaccine immunogenicity, but they have little or no pre-existing naturally acquired immunity to CS antigen through prior exposure to malaria infection. In this group, an inverse association between anti-CS antibody pre-vaccination and

induction of anti-CS through vaccination was expected and confirmed through analyses of Phase 3 data: there was an association between higher post vaccination anti-CS IgG and reduced incidence of clinical malaria (p=0.0003). Infants who were seropositive for anti-CS at baseline (maternal antibodies) had lower post vaccination anti-CS IgG GMT (and a higher clinical malaria incidence (p=0.0001)), consistent with interference between maternally acquired CS antibodies, immunogenicity and protection.

By contrast, in the 5-17 month age category, maternally acquired anti-CS IgG will have decayed, and pre-existing naturally acquired immunity to malaria will have begun to develop. Further, as a result of immune maturation RTS,S/AS01 induces 3-fold higher IgG GMTs in the 5-17 month age category than in 6-12 week age category. In the 5-17 month age category there is no clear correlation between anti-CS IgG and protection against disease. Anti-CS antibody titers at one month post dose 3 were not associated with the incidence of clinical malaria (p=0.2426). Children who were seropositive for anti-CS at baseline experienced a higher incidence of clinical malaria (p=0.0042), perhaps indicating residence in a higher exposure setting. When participants in the 5-17 month age category were grouped by tertile of their vaccine induced anti-CS responses, there was no clear association with efficacy (Figure 5.3), whereas there was some evidence of an association for the 6-12 week age category, although the trend test was not significant.





Taking these findings together, one possible interpretation is that there is an association between anti-CS IgG and protection against disease in the range of GMTs seen at 1 month post dose 3 in the 6-12 week age category, but that at the higher immunogenicity levels seen in 5-17 month age category this association is no longer seen.

Figure 5.3 a-b: Vaccine efficacy by tertile of anti-CS antibody concentration (ATP population) a) 5-17 month age category (R3C, 3-dose schedule), and b) 6-12 week age category (R3C, 3-dose schedule). Error bars represent 95% confidence interval. t1-3: tertile 1-3 of anti-cs titer post vaccination. Provided by GSK on request.

As noted above, immunogenicity is not as high after the fourth dose, as after the third dose. There is no immunogenicity data on a fifth dose.

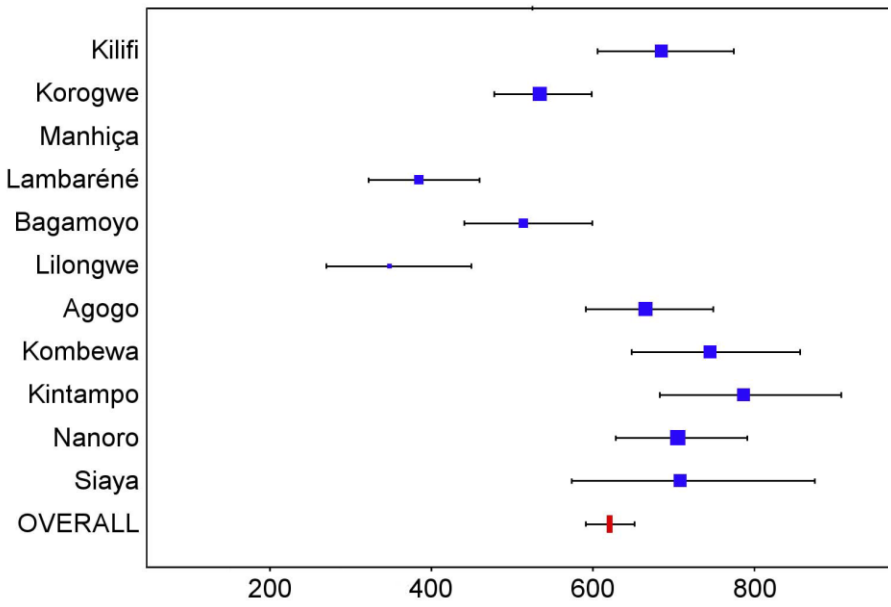


Figure 5.4: Anti-CS antibody geometric mean titres (EU/ml) in RTS,S/AS01 recipients 1 month after dose 3 in children 5-17 months of age at enrolment, ordered by increasing malaria incidence at each trial site (ATP population)[25].

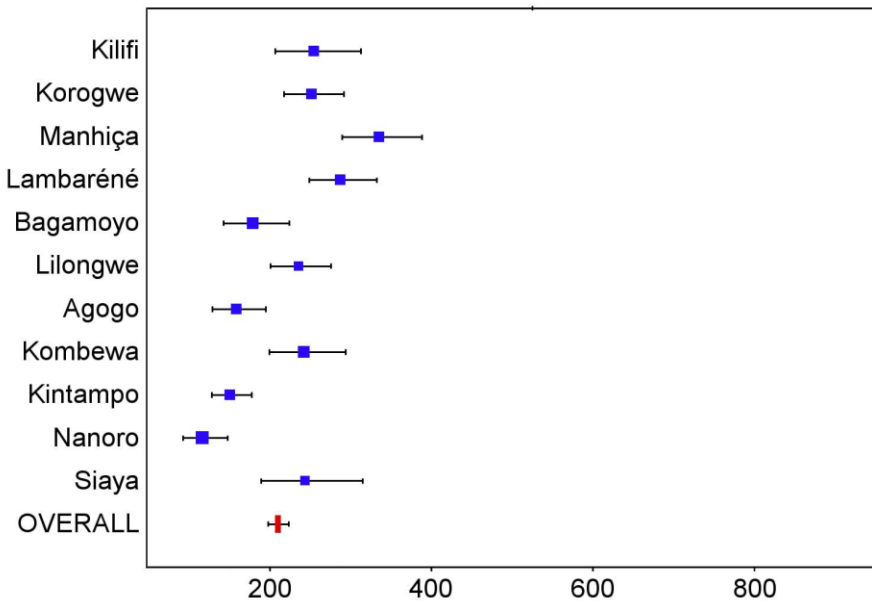


Figure 5.5: Anti-CS antibody geometric mean titres (EU/ml) in RTS,S/AS01 recipients 1 month after dose 3 in children 6-12 weeks of age at enrolment, ordered by increasing malaria incidence at each trial site (ATP population)[25].

Table 5.2: Anti-CS antibody GMT and VE in the 5-17 month age category at 12 months post dose 3 by site, ordered by increasing GMT[25].

Trial site	GMT (LL, UL)	$VE_{2.5\text{-}14M}$ (95%CI)
Lilongwe	348.4 (270.2, 449.2)	53.2 (17.6, 73.4)
Lambaréné	385.0 (322.6, 459.5)	61.7 (28.5, 79.5)
Bagamoyo	514.0 (441.0, 599.0)	73.9 (57.7, 83.9)
Korogwe	534.7 (477.6, 598.5)	62 (23.6, 81.1)
Agogo	665.5 (591.4, 749.0)	60.5 (48.1, 70)
Kilifi	685.2 (606.1, 774.6)	83 (37.2, 95.4)
Nanoro	705.1 (628.6, 791.0)	44 (36.9, 50.4)
Siaya	708.6 (573.8, 875.0)	50 (40.1, 58.2)
Kombewa	745.1 (648.1, 856.6)	46.1 (34.8, 55.4)
Kintampo	787.1 (682.6, 907.6)	50.7 (42.5, 57.7)
OVERALL	**621.0 (591.5, 651.9)**	**51.3 (47.5, 54.9)**

Table 5.3: Anti-CS antibody GMT and VE in the 6-12 week age category at 12 months post dose 3 by site, ordered by increasing GMT[25].

Trial site	GMT (LL, UL)	$VE_{2.5\text{-}14M}$ (95%CI)
Nanoro	116.9 (92.5, 147.9)	27.5 (17.1, 36.5)
Kintampo	151.0 (128.5, 177.4)	-12.1 (-47.9, 15.1)
Agogo	158.6 (129.1, 194.8)	23.7 (0, 41.8)
Bagamoyo	179.1 (143.1, 224.0)	44.7 (-11.2, 72.5)
Lilongwe	235.5 (200.9, 276.0)	55.4 (31.4, 71)
Kombewa	242.3 (199.7, 294.1)	44.4 (25.5, 58.5)
Siaya	244.1 (189.2, 315.0)	38.5 (25.2, 49.5)
Korogwe	252.1 (217.7, 292.0)	46.6 (-26.1, 77.3)
Kilifi	254.4 (206.8, 313.2)	-11.9 (-1146.5, 90)
Lambaréné	287.6 (248.8, 322.3)	13.9 (-209.2, 76)
Manhiça	335.3 (289.5, 388.5)	8.9 (-95.8, 57.6)
OVERALL	**210.5 (198.2, 223.6)**	**32.9 (26.4, 38.9)**

6. RTS,S/AS01 Vaccine Safety

RTS,S/AS01 is a new vaccine, and AS01 has not yet been used in other licensed vaccines. There is clinical experience with AS01 in a number of other non-malaria experimental products, including in over 7,000 adults in a Phase III trial of varicella–zoster virus glycoprotein E and AS01[47]. Nearly 12,500 infants and children have received the RTS,S/AS01 vaccine in clinical trials. The WHO Global Advisory Committee on Vaccine Safety (GACVS) reviewed the safety data for RTS,S/AS01 in 2009, 2014 and 2015 and determined RTS,S/AS01 has an acceptable safety profile[48-50].

The following sections cover the safety results generated from the Phase 3 trial of RTS,S/AS01. Among the first 200 participants enrolled at each trial site for both age categories, unsolicited adverse events within 30 days after vaccination and local and systemic reactogenicity within 7 days after vaccination were collected. Serious adverse events were identified for all participants by

passive surveillance throughout the observation period (48 months in 5-17 month age category, 38 months in 6-12 week age category).

6.1 Reactogenicity

Safety parameters evaluated included reactogenicity observed during the 7 days following vaccination and unsolicited symptoms recorded during 30 days after vaccination with doses 1, 2 and 3 (first 200 subjects enrolled at each site, for each age group).

In the 5-17 month age category, the proportion of unsolicited reports within 30 days of any of the first three vaccine doses were similar between the RTS,S and control groups: 86.1% (95%CI 84.2, 87.8) and 86.8% (95%CI 84.1, 89.2), respectively[51]. Pain, drowsiness, irritability, loss of appetite, and fever ($\geq$37.5^{o}C) were reported more frequently in the seven days following RTS,S compared to control vaccine (Figure 6.1). Fever occurred most frequently and was reported after 31.1% of doses in the RTS,S group (95%CI 29.7, 32.5) compared with 13.4% of doses in the control group (95%CI 12.0, 14.9). Grade 3 fever (>39^{o}C) occurred in 2.5% of participants in the RTS,S group (95%CI 2.1, 3.1) compared to 1.1% in the control group (95%CI 0.7, 1.7).

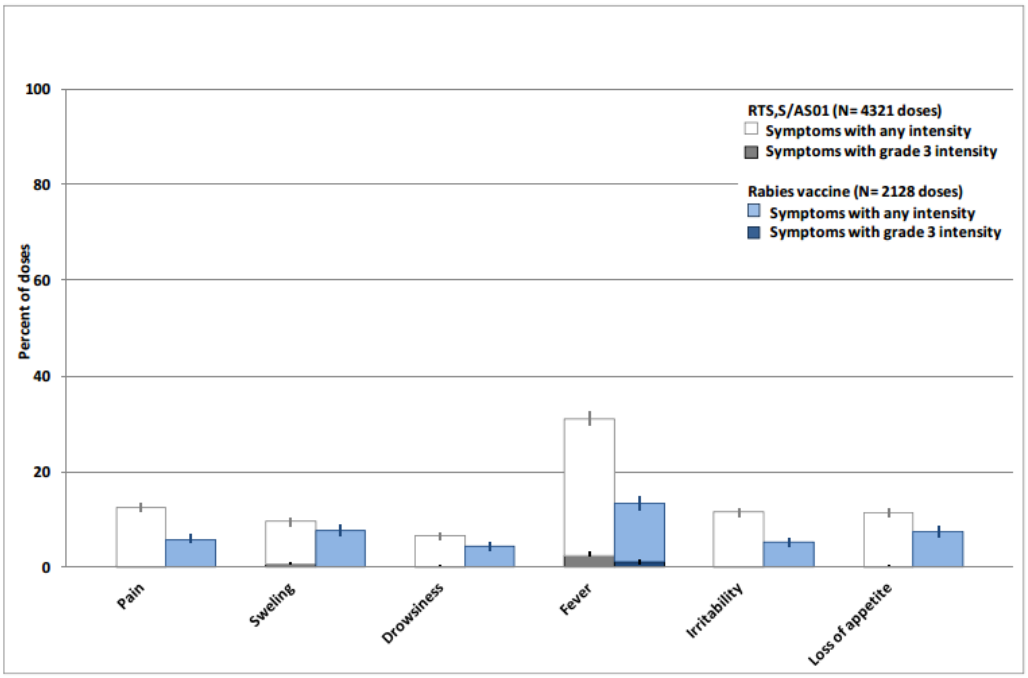


Figure 6.1: Incidence of solicited local and general adverse events reported during the 7-day post vaccination period following each dose in children 5-17 months of age at enrolment (ITT Population, Malaria-055)[51].

In the 6-12 week age category, the proportion of unsolicited reports within 30 days of any of the first three doses co-administered with DTPwHepB/Hib and OPV were similar between the RTS,S and control groups: 79.4% (95%CI 77.2, 81.5) and 81.3% (95%CI 78.3, 84.1), respectively. The proportion of solicited local symptoms (pain, redness, and swelling) was also similar between the RTS,S and control groups (Figure 6.2). The rates of systemic reactions (specifically drowsiness, irritability, and fever) were higher for participants in the RTS,S group compared to the control group. Fever again

occurred most frequently and was reported after 30.6% of doses in the RTS,S group (95%CI 29.2, 32.0) compared with 21.1% of doses in the control group (19.4, 22.8)[26].

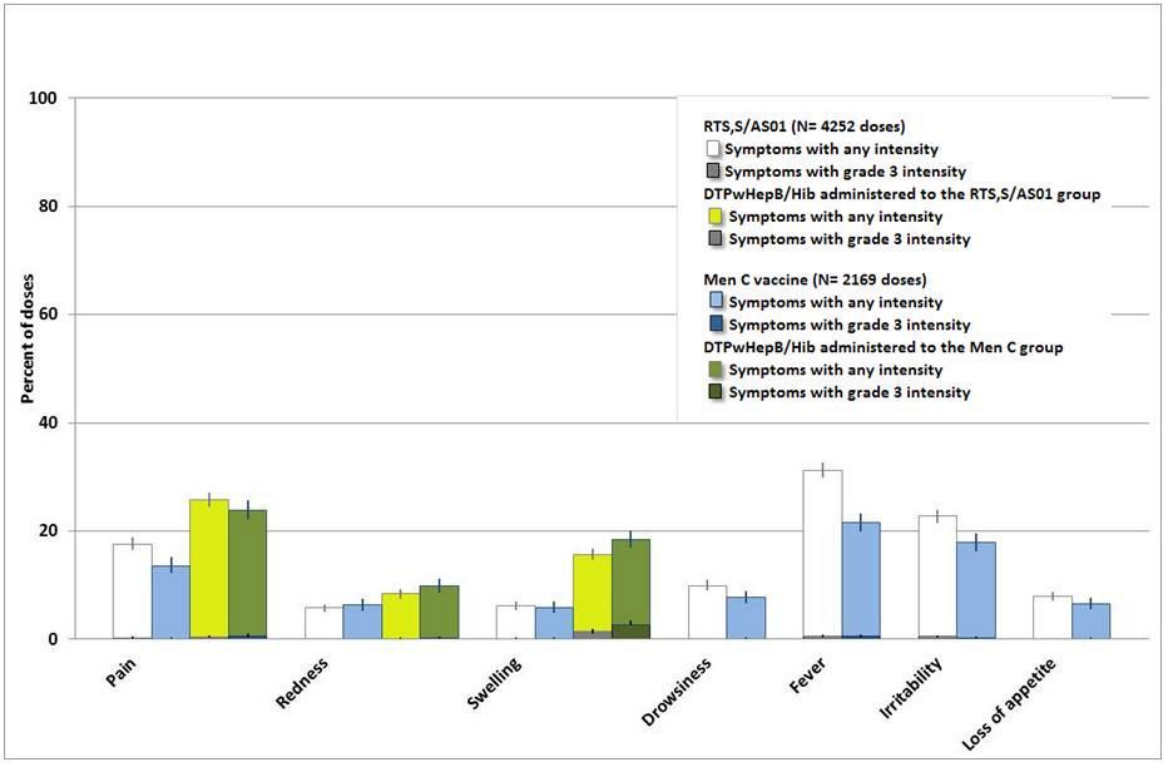


Figure 6.2: Incidence of solicited local and general adverse events reported during the 7-day post vaccination period following each dose in infants 6-12 weeks of age at enrolment (ITT, Malaria-055). Provided by GSK on request.

6.2 Serious adverse events

In the 5-17 month age category, from the first dose to the trial end (M0-SE), Serious Adverse Events (based on MEDRA preferred terms) were slightly less frequent in the RTS,S groups compared to the control group (R3R-24.2%, R3C-25.3%, C3C- 28.4%)(Table 6.1) and this remained so when malaria was excluded as an SAE (R3R-22.6%, R3C-23.7%, C3C- 26.4%). A similar number of deaths occurred in the RTS,S/AS01 groups compared with the control group (R3R-2.0%, R3C-1.7%, C3C- 1.5%). Of the 1472 reported SAEs in the RTS,S/AS01 groups (with and without the fourth dose), 12 were considered related to the vaccine by the investigator (7 seizures, 3 episodes of pyrexia, one episode of myositis, and one injection-site reaction); of the 846 SAEs in the control group, 1 was considered related to the vaccine by the investigator (seizure).

In the 6-12 week age category, from the first dose to the trial end (M0-SE), the frequency of SAEs reported in RTS,S/AS01 groups and the control group were similar (R3R-26.6%, R3C-27.6%, C3C-28.4%) (Table 6.1) and this remained so when malaria was excluded (R3R-25.8%, R3C-26.7%, C3C-27.1%). A similar number of deaths occurred in the RTS,S groups compared with the control group (proportion by group: R3R-2.3%, R3C-2.5%, C3C- 1.9%). Of the 1182 reported SAEs in the RTS,S groups, seven were considered related to the vaccine by the investigator (one injection site reaction,

two episodes of pyrexia, and four episodes febrile convulsions); of the 619 SAEs in the control group, three were considered related to the vaccine by the investigator (two episodes pyrexia and one anaphylactic reaction). The most common SAEs reported in both age categories (>1% of participants) were pneumonia, gastroenteritis, malaria, anaemia, febrile convulsion, and bronchiolitis: the frequency of none of these were statistically significantly different between the RTS,S/AS01 and control groups[26].

Table 6.1: SAEs from first vaccine dose to trial end[24].

5-17 Month Age Category	4-dose schedule (R3R) N=2976		3-dose schedule (R3C) N=2972		Control group (C3C) N=2974	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
At least one SAE	720	24.2 (22.7, 25.8)	752	25.3 (23.7, 26.9)	846	28.4 (27, 30.1)
At least one SAE excluding malaria	673	22.6 (21, 24.2)	704	23.7 (22, 25.3)	784	26.4 (25, 28.0)
At least one fatal SAE	61	2.0 (2, 2.6)	51	1.7 (1, 2.3)	46	1.5 (1, 2.1)
At least one related SAE	8	0.3 (0, 0.5)	4	0.1 (0, 0.3)	1	0.0 (0, 0.2)
Meningitis (any pathogen)	11	0.4 (0, 0.7)	10	0.3 (0, 0.6)	1	0.0 (0, 0.2)
6-12 Week Age Category	**4-dose schedule (R3R) N=2180**		**3-dose schedule (R3C) N=2178**		**Control group (C3C) N=2179**	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
At least one SAE	580	26.6 (25, 28.5)	602	27.6 (26, 29.6)	619	28.4 (27, 30.4)
At least one SAE excluding malaria	562	25.8 (24, 27.7)	582	26.7 (25, 28.6)	591	27.1 (25, 29.0)
At least one fatal SAE	51	2.3 (2, 3.1)	55	2.5 (2, 3.3)	42	1.9 (1, 2.6)
At least one related SAE	6	0.3 (0, 0.6)	1	0.0 (0, 0.3)	3	0.1 (0, 0.4)
Meningitis (any pathogen)	5	0.2 (0.1, 0.5)	7	0.3 (0.1, 0.7)	6	0.3 (0.1, 0.6)

6.3 Adverse events of specific interest

Febrile convulsion had been identified as an adverse event of specific interest in Phase 2 trials. Therefore the Phase 3 trial was designed with proactive collection of data to assess incidence of febrile convulsion within 7 days of vaccination according to the Brighton Collaboration Working Group consensus case definition.

An additional numerical imbalance was identified in the Phase 3 trials of RTS,S/AS01: an excess number of meningitis cases in participants in the 5-17 month age category and an increased risk of febrile seizures in the seven days following vaccination in the same age category. Excess of

meningitis events were not identified during Phase 2 studies. Note that 18 cases of meningitis occurred in the 6-12 week age category, evenly distributed between RTS,S and control groups. Twenty-two cases of meningitis were seen in the 5-17 month age category with an imbalance between RTS,S and control groups.

A list of potential immune mediated disorders were assessed and no imbalance was seen. Given the theoretical concerns associated with a new adjuvant, GACVS consulted with several African experts in autoimmunity, and given the lack of any concerning data from experimental models as well as the infeasibility of surveillance for paediatric autoimmune disorders, for which the epidemiology is largely undetermined, GACVS made no specific recommendation for post-licensure surveillance of auto-immune disorders[50] .

6.3.1 Febrile Seizures

In the 5-17 month age category, the incidence of generalized convulsions (Brighton Collaboration diagnostic certainty level of 1 to 3) within the seven days following any of the first three vaccinations was 1.04 per 1000 doses (95%CI 0.62, 1.64) in the RTS,S/AS01 groups (R3R + R3C) and 0.57 per 1000 doses (95%CI 0.19, 1.34) in the control group (C3C) (Table 6.2), a risk ratio of 1.8 (95%CI 0.6, 4.9). All children who experienced a convulsion reported a history of fever. Twelve of the 18 convulsions in the RTS,S/AS01 groups occurred within 3 days of vaccination; two of the five convulsions in the control group occurred within 3 days of vaccination. Febrile convulsions post-vaccination were not defined as a contraindication per protocol but it was left to the judgment of the investigator to withdraw a subject from further doses if it was considered that remaining in the study would be a risk for the subject.

Following a fourth dose of RTS,S, the incidence of generalized convulsions increased to 2.5 per 1000 doses (95%CI 0.9, 5.3) in the R3R group (Table 6.3). The incidence in the RTS,S group without a fourth dose of RTS,S/AS01 (R3C – received rabies vaccine as control vaccine at 18 months) was still 1.2 per 1000 doses (95%CI 0.3, 3.5), while the incidence in the control group (C3C) was 0.4 (95%CI 0.0, 2.3).

In the 6-12 week age category, the incidence of generalized convulsions within seven days following any of the first three doses was 0.16 per 1000 doses (95%CI 0.02, 0.57) in the RTS,S groups (R3R + R3C) and 0.47 per 1000 doses (95%CI 0.10, 1.37) in the control group (C3C) (Table 6.2), a risk ratio of 0.3 (95%CI 0.1, 2.0). Similarly to the 5-17 month age category, following a fourth dose of RTS,S (R3R group), the incidence was 2.2 per 1000 doses (95%CI 0.6, 5.6); the incidence rates in the R3C and C3C group remained low (Table 6.3).

Table 6.2: Rate of febrile seizures within seven days following any of the first three vaccinations (ITT population). Provided by GSK.

R3R+R3C			C3C			Relative Risk (95%CI)	Risk Difference (95%CI)
N	n	Rate/1000 doses (95%CI)	N	n	Rate/1000 doses (95%CI)		
5 – 17 month age category							
17306	18	1.04 (0.62,1.64)	8728	5	0.57 (0.19,1.34)	1.8 (0.7,4.9)	0.5 (-0.4,1.2)
6 – 12 week age category							
12739	2	0.16 (0.02, 0.57)	6403	3	0.47 (0.10,1.37)	0.3 (0.1, 2.0)	-0.3 (-1.2,0.2)

N: Number of doses; n: number of febrile seizures within 7 days post vaccination;

Table 6.3: Rate of febrile seizures within seven days following the fourth vaccination (ITT population). Provided by GSK and[24].

R3R			R3C			C3C				
N	n	Rate/1000 doses (95%CI)	N	n	Rate/1000 doses (95%CI)	N	n	Rate/1000 doses (95%CI)	Relative Risk (95%CI)	Risk Difference (95%CI)
5 – 17 month age category										
2447	6	2.5 (0.9,5.3)	2472	3	1.2 (0.3,3.5)	2473	1	0.4 (0.0,2.3)	6.1 (0.7,50.3)	2.0 (-0.3,5.0)
6 – 12 week age category										
1825	4	2.2 (0.6,5.6)	1837	0	0.0 (0.0,0.2)	1827	1	0.5 (0.0,3.0)	4.0 (0.5,35.8)	1.6 (-1.2,5.1)

N: Number of doses; n: number of febrile seizures within 7 days post vaccination; Relative Risk and Risk Difference are R3R vs C3C

6.3.2 Meningitis

In the 20 months following the first dose (M0-M20), meningitis was reported as an SAE in 16 of the 5949 5-17 month old participants in the RTS,S groups, and in 1 of the 2974 5-17 month old participants in the control group, a relative risk of 8.0 (95%CI 1.1, 60.3)[25]. In 11 of the meningitis cases (10 in the RTS,S groups and the only case in the control group), no pathogen was identified. Of those cases in the RTS,S groups in which a pathogen could be identified, four were meningococcus, one pneumococcus, and one *Haemophilus influenzae* (Table 6.4). There were six deaths among the meningitis cases (five in RTS,S groups and one in the control group). In the period after the fourth dose until the end of the trial (M21-SE), 2 additional cases occurred in the RTS,S group that received the fourth dose, 3 cases occurred in the RTS,S group that did not receive the fourth dose, and no additional cases occurred in the control group. Of these five cases in the RTS,S groups, two were *Haemophilus influenzae*, one was meningococcus, and one was tuberculosis (no pathogen was identified in one).

Table 6.4: Identified pathogen in the 22 meningitis cases through the duration of the trial in 5-17 month age category (ITT population). Provided by GSK.

Months 0-20	4-dose schedule (R3R) N=2976	3-dose schedule (R3C) N=2972	Control (C3C) N=2974
Meningitis	4	5	1
Meningitis haemophilus	1	0	0
Meningitis meningococcal	3	1	0
Meningitis pneumococcal	0	1	0
Meningitis viral	1	0	0
Meningitis total (17 cases)	**9**	**7**	**1**
Months 21- SE	**4-dose schedule (R3R) N=2681**	**3-dose schedule (R3C) N=2719**	**Control (C3C) N=2702**
Meningitis	1*	0	0
Meningitis haemophilus	0	2	0
Meningitis meningococcal	0	1	0
Meningitis tuberculous	1	0	0
Meningitis total (5 cases)	**2**	**3**	**0**

*1 subject reported the occurrence of meningitis after month 21 in the R3R group but did not receive the fourth dose.

Most sites reported only one or two cases of meningitis during the 48 month follow up period in this age group (Figure 6.3). However, two sites outside of the Meningitis Belt (Lilongwe, Malawi, and Kombewa, Kenya) reported nine and five cases, respectively (64% of total reported in the 5-17 month age category).

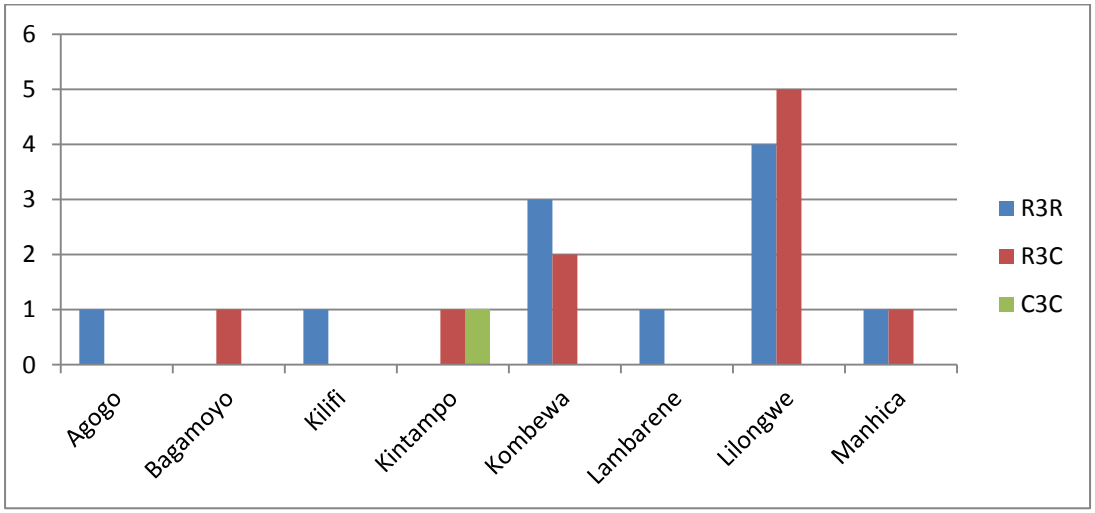
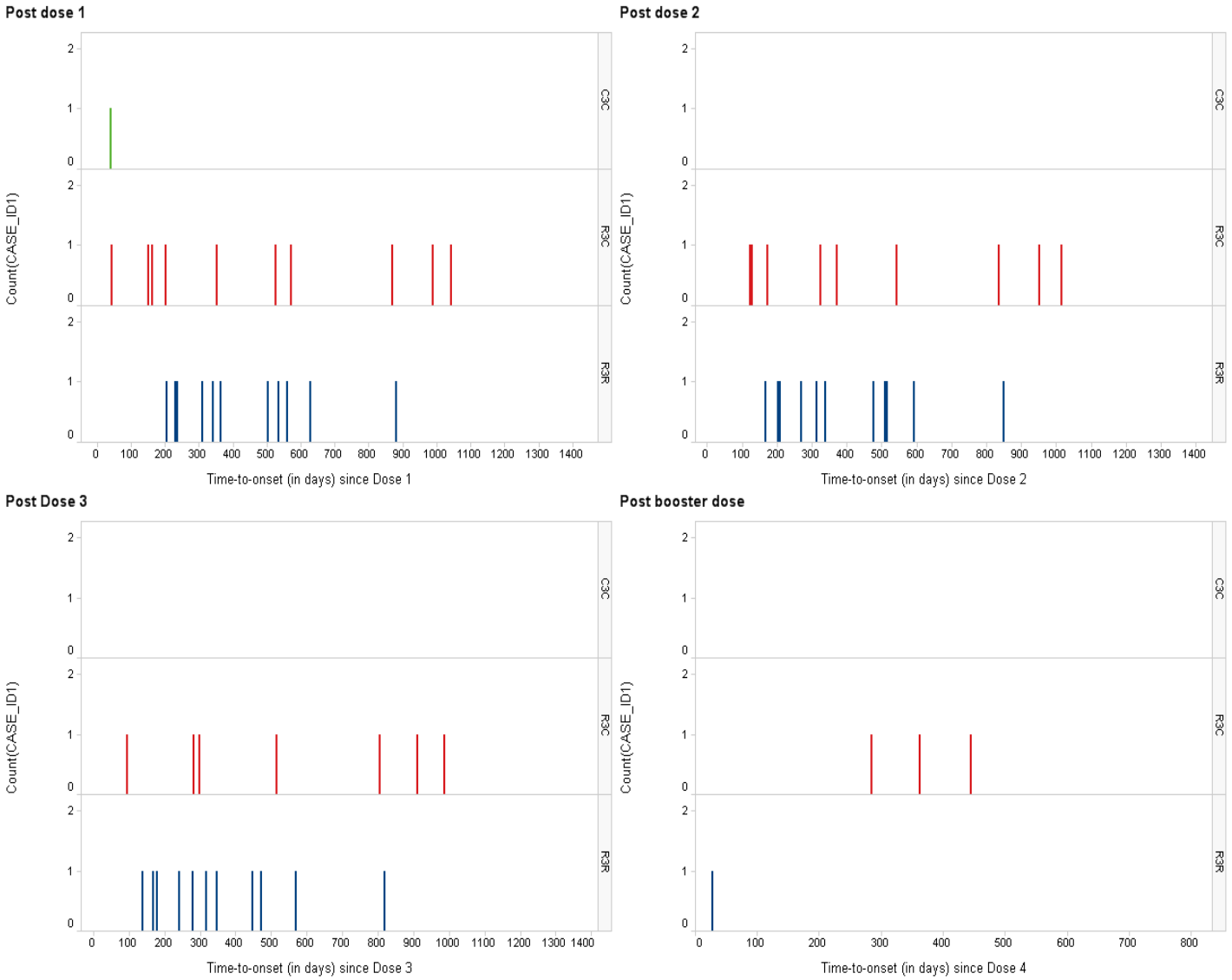


Figure 6.3: Distribution of the 22 meningitis cases in the 5-17 month age category by trial site throughout the complete study period (median 48 months follow-up from dose 1). Provided by GSK.

a) 5-17 months age category (M0-SE; median 48 months follow-up from dose 1)



b) 6-12 weeks age category (M0-SE; median 38 months follow-up from dose 1)

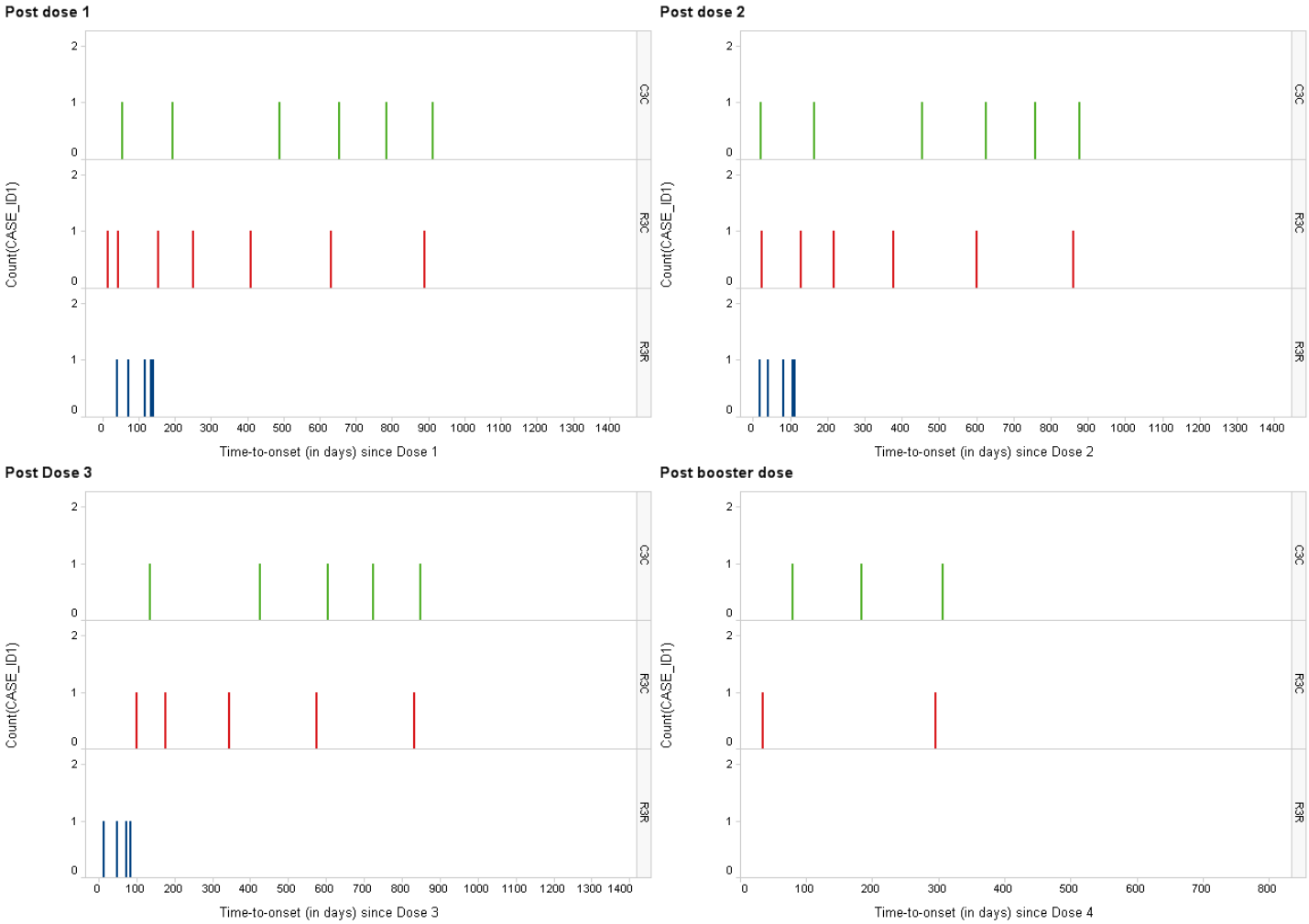


Figure 6.4: Time to onset distribution of meningitis cases following vaccination (any dose), by study group (ITT population). a) 5-17 month age category, b) 6-12 week age category[24].

GACVS reviewed the possible association and determined there was no evidence of temporal clustering in relation to the time of vaccination (Figure 6.4). GACVS ultimately determined meningitis should therefore be regarded as a potential signal which requires further assessment post-licensure[50].

Among participants in the 6-12 week age category, in the 20 months following the first dose (M0-M20), meningitis was reported as an SAE in nine of the 4358 participants in the RTS,S groups, and in three of the 2179 participants in the control group, a relative risk of 1.50 (95%CI 0.41, 5.55). In five of the meningitis cases (three in the RTS,S groups and two in the control group), no pathogen could be identified. Of the remaining seven cases for which a pathogen could be identified, four were pneumococcus and three were salmonella. There were four deaths among the meningitis cases (two in the RTS,S groups and two in the control group). From months 21 to the trial end (M21-SE; median 18 months of follow-up from fourth dose to study end), two additional cases occurred in the RTS,S group that did not receive the fourth dose (one without a pathogen identified, one *Haemophilus influenzae*), three additional cases occurred in the control group (one without a pathogen identified, one *Haemophilus influenzae* and one pneumococcus), and no additional cases occurred in the RTS,S group that received the fourth dose. Of the three *Haemophilus influenzae* cases in the RTS,S group, one participant had documented Hib vaccination, one had no documentation of Hib vaccination, and for one Hib vaccine status could not be determined. In the totality of the trial (M0-SE), the number of meningitis cases in the RTS,S/AS01 groups were similar to those in the control group (R3R: 5, R3C: 7, C3C: 6).

The sponsor coordinated an expert chart review of the meningitis cases. Based on this review, the number of confirmed meningitis cases was reduced (Table 6.5); however, the imbalance between the RTS,S groups and the control group remained in the 5-17 month age group.

Table 6.5: Determination of meningitis cases following expert review in the 5-17 month and 6-12 week age groups. Provided by GSK on request.

5-17 month age group				6-12 weeks age group			
After 3 doses	**R3R**	**R3C**	**C3C**	**After 3 doses**	**R3R**	**R3C**	**C3C**
Confirmed meningitis	5	4	0	Confirmed meningitis	3	4	1
No meningitis	4	2	2	No meningitis	2	2	3
Undetermined	4	2	3	Undetermined	2	0	0
After fourth dose	**R3R**	**R3C**	**C3C**	**After fourth dose**	**R3R**	**R3C**	**C3C**
Confirmed meningitis	1	2	0	Confirmed meningitis	0	1	2
No meningitis	1	2	0	No meningitis	0	0	1
Undetermined	1	0	0	Undetermined	0	1	0

6.4 Summary of safety profile of RTS,S/AS vaccines from Phase 2 studies

Phase 2 studies in children did not identify any concerning safety signals, either for AS01-adjuvanted vaccines[52-55] or for AS02-adjuvanted vaccines[45, 52, 53, 56-59], including when co-administered with EPI vaccines. In a pooled analysis of Phase 2 studies of AS01 and AS02-adjuvanted vaccines, including data on 2,981 infants and children, a similar proportion of participants in the RTS,S/AS and control groups experienced at least one adverse event within 30 days of vaccination (75.0% and 70.2%, respectively)[60]. Upper respiratory tract infections, malaria, pneumonia, and gastroenteritis were reported most frequently. Fewer non-malaria serious adverse events (SAEs) were reported in the RTS,S group (14.9%) compared to the control group (17.7%)(RR=0.81, 95%CI 0.69, 0.95). Five recipients in the Phase 2 trials experienced a seizure within 7 days after RTS,S, which was a similar proportion to that of controls (0.3% of participants). In this pooled analysis, no one SAE occurred at a significantly higher frequency in RTS,S-recipients compared to control vaccine-recipients, including febrile convulsions. Fatal SAEs occurred in 0.7% of RTS,S-recipients, compared to 1.5% of control participants (RR=0.49, 95%CI 0.24, 0.94).

Table 6.6: Meningitis cases reported in Phase II or Phase III studies (excluding Malaria-055). Provided by GSK on request.

Study	Site	Age of case	Gender	Treatment group	Meddra term	Last dose	Time since last dose
Mal-026	Mozambique	3Y	Male	RTS,S/AS02	Meningitis, pyrexia, musculoskeletal stiffness, excoriation	3	299 days
Mal-040	Tanzania	4M	Male	RTS,S/AS02, Tetract-hib	Meningitis viral, pyrexia, fontanelle bulging	2	17 days
Mal-040	Tanzania	4M	Male	Control	Pneumonia, meningitis viral, pyrexia, vomiting, decreased appetite, diarrhoea, crying, dyspnoea, irritability, crepitations, wheezing	2	25 days
		7M*			Pneumonia, meningitis viral, pyrexia, rhinorrhoea, cough, fontanelle bulging, crepitations*	3*	79 days*
Mal-044	Kenya	35Y	Male	Control	Meningitis cryptococcal, HIV infection, headache, photophobia, neck pain, oral candidiasis, asthenia, pulmonary tuberculosis	3	149 days
Mal-044	Kenya	36Y	Male	RTS,S/AS01	Meningitis, HIV infection, hallucination, pyrexia	3	150 days
Mal-044	Kenya	27Y	Female	Control	Meningitis, HIV infection, headache, neck pain, photophobia, pyrexia, cough, oropharyngeal pain, malaise, pallor, lymphadenopathy, pelvic inflammatory disease	3	196 days
Mal-057	Malawi	1M	Male	Control	Pneumococcal sepsis, meningitis pneumococcal	1	8 days
Mal-057	Malawi	7D	Male	RTS,S/AS01, BCG, OPV	Meningitis neonatal, pneumonia	1	7 days
Mal-058	Kenya	3M	Male	Control	Pneumonia, febrile convulsion, sepsis, meningitis haemophilus	1	28 days
Mal-063	Burkina Faso	28M	Female	RTS,S/AS01, OPV, Rotavirus, DTPa+Hib, PCV	Sepsis, anaemia, meningitis streptococcal	2	763 days

*Same patient as preceding row

7. Vaccine Impact

7.1 Estimated cases averted due to RTS,S/AS01

The estimated number of cases averted by RTS,S/AS01 in the trial was the sum of differences in the number of cases between the control and the RTS,S/AS01 groups, expressed per 1000 participants vaccinated.

7.1.1 Cases of clinical malaria averted

In the 18 months following the first three doses (M2.5-M20), 721 cases of clinical malaria were estimated to be averted per 1000 vaccinees (95%CI 591, 847) in the 5-17 month age category compared to 296 (95%CI 179, 413) in the 6-12 week age category (Table 7.1). Among 5-17 month old participants who did receive a fourth dose of RTS,S (R3R), the estimated number of cases of clinical malaria averted by study month 33 (M2.5-M32) and by study end (M2.5-SE) were 1097 (95%CI 894, 1295) and 1239 (95%CI 908, 1552) per 1000 vaccinees. In this same group (R3R) in the 6-12 month age category, the estimated number of cases of clinical malaria averted by study month 33 (M2.5-M32) and by study end (M2.5-SE) were 583 (95%CI 374, 798) and 665 (95%CI 407, 922) per 1000 vaccinees, respectively.

Table 7.1: Cumulative cases of clinical malaria averted per 1000 vaccinees and 95% confidence interval (primary case definition) at months 21, 33, and 48 (ATP population). Provided by GSK on request.

Study month	5-17 month age category		6-12 week age category	
	3-dose schedule (R3C)	4-dose schedule (R3R)	3-dose schedule (R3C)	4-dose schedule (R3R)
M2.5-M20	721 (591, 847)		296 (179, 413)	
M2.5-M32	855 (653, 1053)	1097 (894, 1295)	336 (103, 558)	583 (374, 798)
M2.5-SE	860 (534, 1166)	1239 (908, 1552)	368 (73, 638)	665 (407, 922)

The greatest number of cases averted per 1000 vaccinees were at sites with the highest level of transmission (Figure 7.1). The impact of a fourth dose of RTS,S was largest in these sites as well.

a) 5-17 month age categories **b) 6-12 week age category**

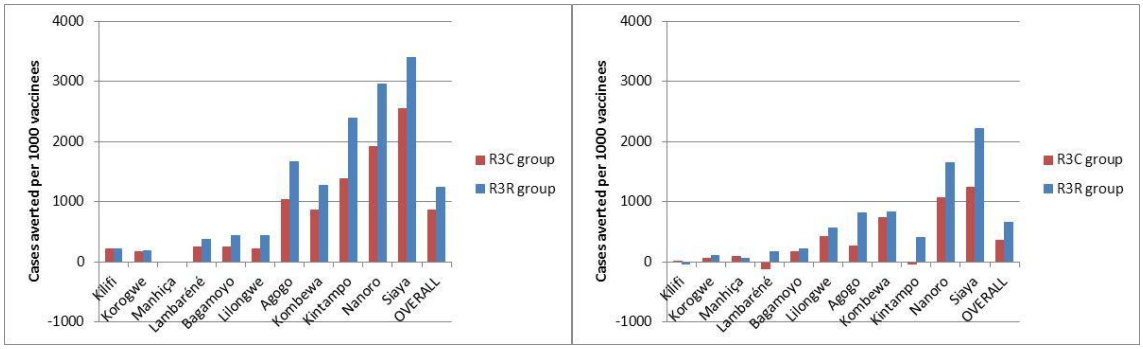


Figure 7.1: Cases of clinical malaria averted per 1000 vaccinees at each site for M2.5-SE (ATP population, primary case definition). Sites are ordered based on incidence of clinical malaria (secondary case definition) measured in control infants 6-12 weeks of age at enrolment during 12 months of follow up. Provided by GSK on request.

7.1.2 Cases of severe malaria averted

At 18 months following the first three doses (study month 21), 16 cases of severe malaria were estimated to be averted per 1000 vaccinees (95%CI 5, 27) in the 5-17 months group compared to 4 (95%CI -8, 16) in the 6-12 weeks age group (Table 7.2). Among 5-17 month old participants who did receive a fourth dose of RTS,S (R3R), the estimated number of cases of severe malaria averted at study month 33 and at study end were 15 (95%CI 1, 29) and 13 (95%CI -3, 29) per 1000 vaccinees. In this same group (R3R) in the 6-12 months group, the estimated number of cases of severe malaria averted at study month 33 and at study end were 12 (95%CI -4, 28) and 13 (95%CI -4, 30) per 1000 vaccinees.

Table 7.2: Cumulative cases of severe malaria averted per 1000 vaccinees and 95% confidence interval (primary case definition) at months 21, 33, and study end (ATP population). Provided by GSK on request.

Study month	5-17 month age category		6-12 week age category	
	3-dose schedule (R3C)	4-dose schedule (R3R)	3-dose schedule (R3C)	4-dose schedule (R3R)
M2.5-M20	16 (5, 27)		4 (-8, 16)	
M2.5-M32	7 (-9, 23)	15 (1, 29)	4 (-13, 22)	12 (-4, 28)
M2.5-SE	0 (-18, 17)	13 (-3, 29)	6 (-12, 26)	13 (-4, 30)

7.2 Estimated vaccine impact using mathematical modelling

In 2010, WHO initiated an extensive comparison exercise of four mathematical models (Imperial College, Swiss Tropical and Public Health Institute, Institute for Disease Modelling and GlaxoSmithKline) to estimate the public health impact and cost-effectiveness of RTS,S/AS01 in a range of scenarios. The current status of this work and outcomes so far are reported here. Aggregate site-specific clinical efficacy and disease incidence data from the phase III trial were made available to the modelling groups before publication. This data was used for parameterising

the vaccine impact component of the models. Additionally, Imperial College had access to individual participant data including antibody levels from the trial to inform their models. For population predictions, the modelling groups were asked to consider a 6, 7.5, 9 months schedule with and without a fourth dose at 27 months (18 months after dose 3). Following a recommendation from the WHO JTEG/IVIR-AC subgroup overseeing the process, the time horizon for impact evaluation was set at 15 years. The models explore RTS,S/AS01 impact under a set of harmonised assumptions, including demography, access to effective malaria treatment, and a range of transmission intensities (described by Plasmodium falciparum parasite prevalence in 2-10 year olds, $PfPR_{2-10}$). Incremental cost-effectiveness ratios (ICERs) were calculated using a single set of agreed costs and a harmonised methodology to enable comparative outputs from the four models. As a further step, the impact of RTS,S/AS01 in six African countries, with varied malaria transmission intensity and seasonality, was assessed under largely non-harmonised conditions (except for costing, vaccine coverage, demographics and and $PfPR_{2-10}$ estimates provided by the Malaria Atlas Project).

Although not assessed directly in the trial, RTS,S mode of action is protection against malaria infection and vaccine impact is therefore modelled as efficacy against infection in all the models (the proportion of blood-stage infections prevented). All four models demonstrated good fits to the clinical efficacy and consistently estimated RTS,S/AS01 to have high initial efficacy against infection in children vaccinated between 5 and 17 months of age immediately following the third dose, with initial efficacy ranging from 75% to 95% against infection. This efficacy is estimated to wane rapidly in the first 12 months. All models predict low efficacy beyond 12 months but with variation in the rate of decline over time due to different assumptions regarding the shape of the waning profile and different assumptions in translating efficacy against infection into protection against clinical malaria. In all four models the fourth dose is found to increase protection against infection to a level that is lower than the initial protection. All four models predict a faster decay in vaccine efficacy against clinical disease at higher transmission levels due to the combined effects of waning of vaccine efficacy against infection and different rates of acquisition of natural immunity in the vaccine and control arms.

A comparison of the models in the absence of vaccination showed some differences in baseline disease burden which are largely attributable to differences in case definition and assumptions underlying immunity acquisition. Although largely consistent in age patterns of underlying burden with transmission intensity, with differences in magnitudes related to case definitions and data used to a parameterise the models, at very high transmission settings (> 65% prevalence) there is divergence between the models in the predicted pattern of burden. This divergence impacts the estimate of cases and deaths available for a vaccine to avert. In very high transmission settings some modelling groups predict that a reduction in transmission may temporarily and marginally increase the number of cases and subsequent deaths due to a change in the age distribution of malaria deaths. Other groups predict that a reduction in transmission intensity would always be associated with either no change in malaria deaths (because the exposure is so high in high transmission settings) or a reduction in malaria deaths. The data to support either prediction are limited

In all models vaccination is predicted to lead to an age shift in malaria incidence. In high prevalence

settings this is predicted to occur sooner than moderate or low transmission settings. The age-shift is predicted to occur sooner for more severe disease endpoints compared to uncomplicated cases. Given the rapid waning of protection of RTS,S in the absence of a fourth dose, the age shift is predicted to occur soon after vaccine introduction. This predicted effect is general to any preventive malaria intervention, and indeed a more pronounced age shift is predicted for seasonal malaria chemoprevention.

The two models that were designed to include indirect effects of vaccination predict little herd protection from RTS,S/AS01 vaccination when introduction is limited to this age group and transmission remains moderate, given the role of infected individuals of all ages in contributing to transmission. One of the two models predicts a substantial indirect effect at low transmission ($PfPR_{2-10}$ < 5%).

The JTEG/IVIR-AC subgroup noted that in the pivotal Phase 3 trial a similar cumulative incidence of severe malaria was reported in the arm that received RTS,S/AS01 without the fourth dose compared to the control arm. This could be interpreted as in apparent conflict with the predictions of the models that RTS,S will have a small but consistently overall positive impact against severe malaria and malaria-related mortality both with and without a fourth dose (even with an age shift). Reasons for such apparent discrepancies include that the efficacy against severe malaria when calculated from clinical trial data is strongly biased towards high intensity transmission settings and that confidence bounds around this estimate span the impact that is predicted by the models. Further it was noted that efficacy estimates against malaria hospitalization and all-cause hospitalization are positive in the ITT analyses for the Phase 3 trial, even without a fourth dose.

In the analysis of six anonymised African countries, transmission intensity was found to be a reasonable predictor of public health impact and cost-effectiveness (Figure 7.2). Results aligned closely with those under harmonised assumptions at the respective transmission, although where differences were evident it was due to model country assumptions concerning transmission heterogeneity and health system factors such as high access to effective antimalarial treatment.

All models predict a substantial additional public health impact of RTS,S in settings with $PfPR_{2-10}$ between 10% and 65% (Table 7.3). Below 10% $PfPR_{2-10}$ the models predict smaller positive impacts down to 5% $PfPR_{2-10}$. Furthermore the predictions diverge between the models below 10%. 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. The median of the four model predictions for the costs of routine RTS,S vaccination in a schedule including a fourth dose is 82 USD per DALY averted (assuming 5 USD vaccine costs per dose) in settings with $PfPR_{2-10}$ between 10% and 65% and costs do not exceed 260 USD per DALY averted for $PfPR_{2-10}$ at transmission levels down to 5% PfPR2-10. A 3-dose series without a fourth dose is predicted to be associated with similar costs per DALY averted.

Recently updated MAP (Malaria Atlas Project, the most extensive effort to map malaria parasite prevalence in Africa) estimates show that in many African regions the transmission of *Plasmodium falciparum* malaria has been reduced to $PfPR_{2-10}$ levels below 10% in recent years (see Figure 2.1). In these low transmission settings RTS,S/AS01 is predicted to be less cost effective than in settings with

more intense malaria transmission. Differences between model estimates are also larger at $PfPR_{2-10}$ levels below 10%.

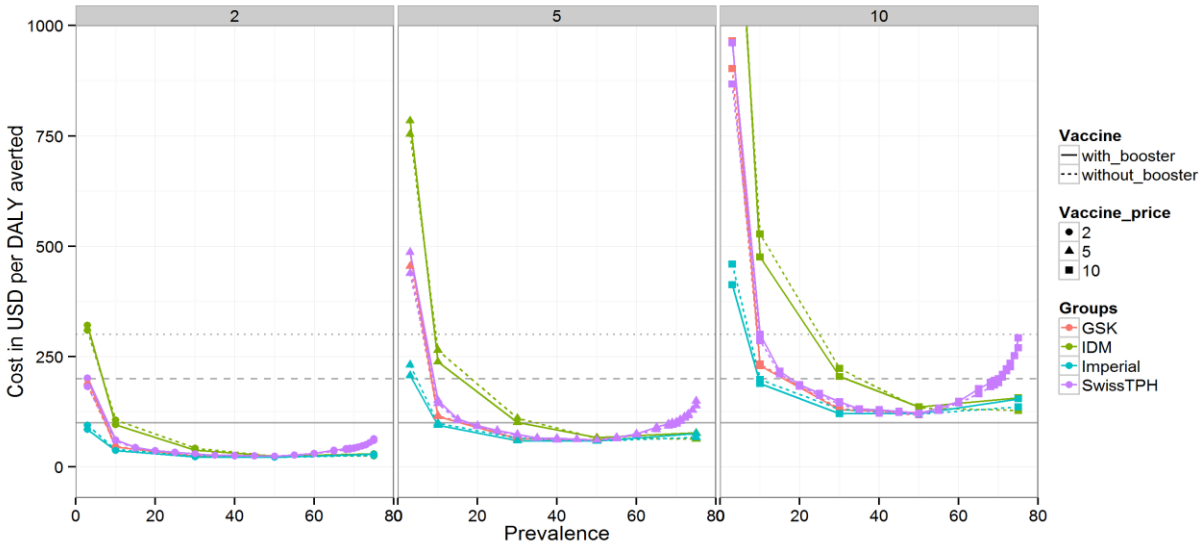


Figure 7.2: Cost (USD) per DALY (median) over 15 years of use of RTS,S via 6-9 month immunisation schedule with and without fourth dose. Columns indicate an assumed vaccine price of either $2, $5, or $10 and colour indicates models (green EMOD DTK (IDM), red GSK, blue Imperial, purple OpenMalaria (SwissTPH)). An immunisation schedule of three doses between 6 and 9 months of age is indicated by dashed lines, and a schedule including the fourth dose by solid lines. Similar ICER estimates were obtained for the schedules with and without a fourth dose because the additional public health benefit of the 4-dose schedule is offset by the incremental cost of implementing the additional dose. The grey reference lines correspond to $100, $200 and $300 per DALY averted by solid, dashed and dotted lines respectively. The cost per DALY averted for the 6-9 month immunisation schedule with 4 doses is the average cost-effectiveness ratio, and not incremental to three-dose schedule. Uncertainty estimates that surround the model predictions are omitted for readability, but overlap one another.

In addition to the harmonised analysis, some individual group predictions compared the cost-effectiveness of RTS,S/AS01 and other malaria interventions. Considered as a package of interventions, RTS,S/AS01 at $5 a dose is likely to be less cost effective than the use of either bed nets or SMC (where applicable) at reducing incidence in children under 5 years up to usage levels around 60-80% for LLIN. Above 60-80% LLIN usage, the costs of achieving greater coverage may become increasingly non-linear with diminishing returns of increased usage for increasing disbursements. This work was not harmonised amongst the groups and further updates on this work would be desirable.

In summary, despite using different model structures and different data sources to supplement the RTS,S/AS01 phase III trial data, estimates of the public health impact and cost-effectiveness of the RTS,S vaccine delivered at 6-9 months of age were consistent for a wide range of transmission settings and indicate a significant public health impact and high level of cost-effectiveness in those settings if implemented after achieving high LLIN usage. Thus, from the health economic perspective, access to LLINs, RDTs and ACT drug courses should be prioritized. In settings where these have been achieved, and where transmission remains above 5-10% $PfPR_{2-10}$ RTS,S/AS01 may be a reasonable

use of resources from both malaria control and immunization perspectives. Given that malaria transmission varies greatly within a country, this also implies, that from a health economic perspective malaria vaccine introduction decisions may need to be made at a subnational level.

From the health economic perspective, in areas of west Africa that are currently recommended by WHO for SMC implementation, it would be more cost-effective to implement SMC first (in addition to LLIN, access to RDT and ACT), and then reassess whether the remaining disease burden justifies consideration of RTS,S/AS01 introduction.

For a comparative review of the cost-effectiveness of malaria vaccine interventions, see *Comparison of the cost effectiveness of LLINs, SMC, the RTS,S vaccine and RTS,S plus IPTi in African settings* (Winskill *et al*, unpublished).

Table 7.3: Estimated deaths per 100,000 fully vaccinated children (FVC) and Incremental Cost Effectiveness Ratios (ICERs) at $5 (USD) per dose. Estimates are presented as median and ranges across the models in parentheses.

Outcome	*Pf*Pr$_{2-10}$ 10% to 65%	*Pf*Pr$_{2-10}$ 30% to 50%	*Pf*Pr$_{2-10}$ 10%	*Pf*Pr$_{2-10}$ 7.5%	*Pf*Pr$_{2-10}$ 5%
3-dose schedule					
Deaths averted per 100,000 FVC	394 (127-708)	451 (287-708)	205 (127-251)	146 (106-225)	100 (74-178)
ICER at $5 dose	$80 ($44-279)	$65 ($49-82)	$139 ($117-279)	$189 ($130-334)	$283 ($159-500)
4-dose schedule					
Deaths averted per 100,000 FVC	484 (189-859)	534 (406-859)	229.5 (189-344)	162.5 (147-297)	106.5 (102-249)
ICER at $5 dose	$87 ($48-244)	$73.5 ($49-96)	$158 ($105-244)	$214 ($120-312)	$316 ($143-462)
Incremental impact					
Proportion of additional deaths averted per 100,000 FVC[a]	22% (3%-49%)	22% (6%-41%)	20% (3%-49%)	28% (-2%-42%)	33% (-8%-40%)

[a]by 4-dose schedule compared to 3-dose schedule

7.2.1 Cost-effectiveness of other "recent" vaccines

Summary figures for the cost-effectiveness of other vaccines in Gavi-eligible countries are provided for comparison. Cost-effectiveness has been estimated to be about $42 ($31-$64) per DALY averted for rotavirus vaccine, priced at $1.50-7.50 per dose[61], $100 per DALY averted for 7-valent pneumococcal conjugate vaccine, priced on $5 per dose[62], and $400 ($200-$500) per DALY averted for HPV vaccine, based on $25 per vaccinated girl[63]. However, care should be taken when making inter-vaccine comparisons as the cost-effectiveness of each vaccine is evaluated using different models and hence is based on different modelling assumptions.

8. Additional Scientific Considerations

8.1 Herd protection/effect on transmission

In principle, pre-erythrocytic vaccines such as RTS,S/AS01 could have a beneficial effect on malaria parasite transmission through blocking the malaria life-cycle at the point of human infection from mosquitoes. However in order for substantial transmission effects to occur, coverage with the vaccine would need to be high in the group that transmits malaria to mosquitoes, including older children and adults. Unlike for some vaccine-preventable diseases, it is known that adolescents and adults contribute significantly to onward transmission of malaria parasites. While older children and adults suffer little severe morbidity in a population under stable and moderate to high transmission, this age group still contributes significantly to malaria parasite transmission. The degree of vaccine efficacy would also be very important for transmission effects. Given the relatively modest efficacy of RTS,S/AS01 and the fact that only a small proportion of the infectious reservoir (i.e. young children) are considered for vaccination it is not expected that there will be any substantial transmission reduction effect from paediatric vaccination with RTS,S/AS01. Malaria parasite transmission models do predict that RTS,S/AS01 could have substantial transmission effects when used in a mass immunization approach in areas with fairly low malaria transmission (entomological inoculation rate less than 10). However a first step before any policy recommendation for such a use would be safety and proof-of-concept of efficacy against infection with RTS,S/AS01 in a wide age range from childhood to adolescents and young adults. As there are no clinical trial data to support this use, the potential indication is not discussed further here.

8.2 Safety and efficacy in special populations

A trial in Kenya evaluated safety and immunogenicity of three doses of RTS,S/AS01 (administered on a 0/1/2 month schedule) in 200 HIV-infected children from 6 weeks to 17 months of age (80% in 5-17 month age range; HIV stage I and II) (Data provided by GSK on request). Children were randomized 1:1 to receive RTS,S/AS01 or a control vaccine (rabies). EPI vaccines were given at least 7 days apart from RTS,S/AS01. At the time of the first vaccine dose, 92% of participants were taking co-trimoxazole; and by one month following dose 3, 97% were on anti-retroviral therapy (up from 73% at the initiation of the trial).

RTS,S/AS01 was immunogenic among the 99 participants who received the experimental vaccine (anti-CS antibody GMC of 329 EU/mL at 1 month post dose 3). Vaccine efficacy against clinical malaria was estimated over 12 months post dose 3 and was 37.2% (95% CI: -26.5%, 68.8%, ATP cohort). During this observation period, one episode of severe malaria occurred in the RTS,S/AS01 group compared to eight episodes in the rabies vaccine group.

In the first 30 days post vaccination, at least 1 SAE was reported in 20.2% (95% CI: 12.8 to 29.5) of subjects in the RTS,S/AS01 group and 11.9% (95% CI: 6.3 to 19.8) of subjects in the rabies vaccine group. During this time period, there were 13 cases of pneumonia in the RTS,S group and 5 cases in the control group (Table 8.1). By 14 months following the first dose, there were 23 total pneumonia cases in each group. During these 14 months, the proportion of participants reporting at least one SAE was similar in the RTS,S and control groups at 41.4% (95% CI: 31.6, 51.8) in the RTS,S/AS01

group and 36.6% (95% CI: 27.3, 46.8) in the rabies vaccine group. The most common SAEs reported were pneumonia, gastroenteritis, and febrile convulsions. Of nine fatal SAEs, five occurred in the RTS,S group and 4 in the rabies vaccine group, none of which were judged to be related to vaccination. Unsolicited AEs occurred in a similar proportion of subjects in both groups in the 30 days post-vaccination (99%). There was no significant difference between growth parameters.

Table 8.1: Most frequent SAEs within 30 days and 14 months following the first dose by treatment group. Provided by GSK on request.

	Within 30 days		Within 14 months	
SAE	RTS,S/AS01 (N=99)	Control (rabies) (N=101)	RTS,S/AS01 (N=99)	Control (rabies) (N=101)
At least one SAE	20	12	41	37
Pneumonia	13	5	23	23
Gastroenteritis	8	7	21	19
Febrile convulsions	6	3	10	13

There was also no significant difference between the RTS,S and rabies vaccine groups on $CD4^+$ T-cell percentage, $CD4^+$ T-cell absolute counts and WHO AIDS clinical classification. There was no difference in HIV viral load reduction between the two groups by 12 months post dose 3, though there was a trend for a more marked reduction in HIV viral load at 1 and 6 months post dose 3 in the rabies group (not statistically significant).

Reactogenicity among HIV-infected participants was compared to that observed in the Phase 3 trial. There was a trend for higher reactogenicity among HIV-infected participants (Table 8.2).

Table 8.2: Reactogenicity of RTS,S/AS01 in HIV-infected participants in two trials. Provided by GSK.

	Special study Malaria-058 (HIV-infected)		Phase 3 Malaria-055 (5-17 months)	
	RTS,S/AS01	Control	RTS,S/AS01	Control
Pain	18.1%	6.0%	12.4%	5.8%
Redness	6.9%	3.0%	3.1%	2.7%
Swelling	10.8%	4.4%	9.6%	7.6%
Drowsiness	11.1%	5.0%	6.6%	4.4%
Fever	47.1%	18.8%	31.1%	13.4%
Irritability	25.3%	10.7%	11.5%	5.3%
Loss of appetite	17.7%	8.7%	11.4%	7.4%

Within the pivotal Phase 3 trial there was no systematic screening for HIV in all participants. Some children were tested on clinical grounds and through this process, there were 51, 54, and 48 HIV-infected participants identified in the R3R, R3C, and C3C groups, respectively. By 32 months post dose 3, 14 had died from each group. Similar proportions experienced at least one SAE by visit 32 (excluding malaria): 92.2% (95%CI 81.1, 97.8) in the R3R group, 83.3% (95%CI 70.7, 92.1) in the R3C group, and 87.5% in the C3C group (95%CI 74.8, 95.3). Febrile convulsions occurred in 11.8% (95%CI 4.4, 23.9), 9.3% (95%CI 3.1, 20.3), and 6.3% (95%CI 1.3, 17.2) in the R3R, R3C, and C3C groups, respectively.

9. Programmatic Considerations

WHO conducted an assessment of programmatic considerations for introduction of RTS,S/AS01 with a first dose at 5 months. This assessment may be found in the document *"Programmatic Options for Implementation of RTS,S Malaria Vaccination Schedule"*.

9.1 Co-administration with routine infant vaccines

RTS,S/AS01 has been evaluated together with EPI vaccines in a randomized, open-label, Phase 2 trial in Ghana, Tanzania, and Gabon. Five-hundred eleven children were randomized to receive RTS,S/AS01 on a 0/1/2 month schedule or a 0/1/7 month schedule. DTwP,/HepB/Hib+OPV was co-administered at visits 0/1/2, and measles and yellow fever was administered at month 7.

The safety results were consistent with other Phase 2 trials. Serious adverse events occurred in 33.5% of participants in the 0/1/2 RTS,S administration schedule (95%CI 26.5, 41.2), 27.6% in the 0/1/7 RTS,S administration schedule (95%CI 21.1, 35.0), and 28.7% in the control group (95%CI 22.0, 36.1). No serious adverse event was judged to be related to vaccination[64]. Non-inferiority criteria were met for all EPI antigens (diphtheria, tetanus, and polio) with the exception of polio 3, for which antibody titres were lower[55]. Of note, the rate of response to polio 3 was comparable between the RTS,S co-administration group and the non-RTS,S group when the titres at screening were taken into account. OPV responses were retested in the Phase 3 trial and non-inferiority criteria were met. Anti-CS GMTs were lower one month following the third dose of RTS,S co-administered with measles at month 7 (107.8 EU/mL) than one month following the third dose of RTS,S co-administered with DTwP,/HepB/Hib+OPV at month 2 (190.3 EU/mL).

Vaccine efficacy was assessed at 19 months[64]. In the 0/1/2 month RTS,S administration group, vaccine efficacy against all clinical episodes from 16.5 months follow up was 60.6% (95%CI 33.3, 76.7). There was no difference in vaccine efficacy in the 0/1/2 or 0/1/7 RTS,S administration schedules in the 1 year after dose 3; vaccine efficacy was estimated as 58.7% (95%CI 30.7, 75.3) and 58.7% (95%CI 32.0, 74.9), respectively.

In another co-administration trial in Ghana, RTS,S/AS01 was co-administered with EPI antigens, including pneumococcal conjugate vaccine (PCV10) and rotavirus vaccine (Data provided by GSK on request). Non- inferiority criteria were met for pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 19F and 23F, but not for 18C, which is a minor serotype in Africa.

Non-inferiority was also demonstrated for co-administration with rotavirus vaccine. Regarding anti-CS antibodies, anti-CS GMT was 205.5 EU/ml when RTS,S/AS01 was co-administered with the basic EPI vaccines (DTPa/Hib + OPV) alone, 188.5 EU/ml when RTS,S/AS01 was co-administered with basic EPI and rotavirus vaccine, and 142.2 EU/ml when RTS,S/AS01 was co-administered with basic EPI and pneumococcal conjugate vaccine. Of note, during a 7-day follow up period after each vaccine dose, fever occurred in 26.4% of participants in the PCV10/RTS,S/EPI group, in 13.7% of participants in the rotavirus/RTS,S/EPI group, and in 14.2% in the RTS,S/EPI group. Without RTS,S, rates of fever were 13.9% in the PCV/HepB/EPI group and 7.8% in the rotavirus/HepB/EPI group. No febrile convulsions were reported.

RTS,S/AS01 was also co-administered with DTPwHepB/Hib+OPV in the 6-12 week group in the Phase 3 trial, contributing to the safety database for co-administration.

10. Overall JTEG assessment and summary of key recommendations for SAGE/MPAC consideration

The first malaria vaccine has been successfully evaluated in a Phase 3 trial. The trial was executed to a very high quality and met its primary endpoint. In the trial, the overall benefit-risk was positive. This vaccine represents a potentially important tool to decrease malaria morbidity and mortality when used together with existing malaria interventions.

Because the trial was executed with high adherence to the protocol, replicating the results with respect to timely vaccination and coverage with a fourth dose may be difficult when the vaccine is administered in the context of a routine immunization program. The trial was also done in the context of very good access to health care. It is necessary to ensure a positive benefit-risk in the context of large scale deployment and routine use.

10.1 JTEG assessment of vaccine efficacy and vaccine schedule, including rebound

Rationale for age category

In the 5-17 months age category without a fourth dose, through the duration of follow-up, the vaccine conferred significant protection against clinical disease. While at the end of the observation period the incidence of clinical malaria was similar to that in the control group, overall, there was a beneficial effect. An analysis of vaccine efficacy by month of age at vaccination in the 5-17 month group showed no variation in efficacy within this age category. Vaccination at earlier ages in this age window (e.g., starting at 5 months) would prevent more early cases of malaria than initiating vaccination at a later age in this 5-17 month window.

In the 6-12 week age category, the vaccine when administered in the EPI schedule had lower vaccine efficacy, both after the first three doses and fourth dose, compared to giving it in the 5-17 month age category. Similarly to the 5-17 month group, the time-stratified efficacy results in infants suggest a higher level of efficacy immediately following vaccination that declines steadily, with essentially no remaining efficacy against clinical malaria by 2.5 years following the initial three doses.

In summary, vaccine efficacy was notably lower in the 6-12 week age category compared to the 5-17 month age category. Observed efficacy when given to 6-12 week infants does not meet any of the efficacy thresholds discussed in the malaria vaccine roadmap. With the introduction of other malaria control measures, the burden of disease is shifting to older age groups, so fewer cases will occur prior to vaccination if the vaccine is administered outside the EPI schedule than would historically have been the case.

Rationale for schedule

Vaccine efficacy results by interval since vaccination suggest a high level of efficacy immediately following vaccination with three doses that declines steadily, with essentially no remaining efficacy against clinical malaria after a few years.

Among those in the 5-17 months age category who received a fourth dose of RTS,S, additional protection against clinical malaria was conferred that appeared to decline in the period following the fourth dose in a way similar to that seen following the first three doses. Thus, the impact on clinical malaria with a fourth dose would be greater than without a fourth dose. Given the evidence of waning immunity following the fourth dose, it is possible that there is little or no protective effect remaining against clinical malaria 18 months after the fourth dose.

Among 5-17 months participants who only received three doses of RTS,S, there was an initial reduction in severe malaria, but this was balanced by an increase in severe malaria around 18 months after the initial vaccine course. Such an effect is sometimes referred to as rebound. Rebound refers to higher susceptibility to severe malaria among recipients of a malaria-control intervention (in this case the RTS,S vaccine) when the intervention is withdrawn (when vaccine-induced immunity wanes) compared to contemporaneously-followed individuals in the same population who did not receive the intervention.

This rebound effect for severe malaria was most marked in higher transmission settings, possibly because participants in the control group developed immunity through natural infection more rapidly – the malaria vaccine reduced the number of clinical episodes, which in turn reduced acquisition of naturally acquired immunity. Importantly, a rebound effect for severe malaria was not observed among children vaccinated at 5-17 months of age who received four doses of vaccine up to the end of follow-up, or in the group vaccinated at 6-12 weeks in whom vaccine efficacy was lower and prevented fewer episodes of malaria. It is not known if there will be any rebound effect following waning of immunity after the fourth dose in the 5-17 months group. Reassuringly, the trial showed that the incidence of severe malaria is markedly reduced in those in the 5-17 month age category when measured towards the end of the trial in both vaccine and control groups, when children had reached the age of 4 years or so.

Given the evidence of a rebound effect for severe malaria in children vaccinated at 5-17 months of age who did not receive a fourth dose, a fourth dose would seem to be essential. Its feasibility must be considered in the planning phase of vaccine introduction, with realistic consideration of coverage attainable.

The four dose schedule had a notable impact on clinical malaria, severe malaria, and all-cause hospitalizations. In the 5-17 month group, it was estimated that, on average across the trial sites, 1239 (95%CI 908-1552) cases of clinical malaria were averted per 1000 fully vaccinated over 48 months. Thirteen cases of severe malaria (95%CI -3, 29) and 44 hospitalizations (95%CI 0, 86) were estimated to have been averted under the same parameters. The number of cases averted was substantially lower for the 3-dose schedule and in infants.

Additional considerations

One or more further doses (e.g., fifth) may be desirable. It is critical to obtain data on the effects of further doses, both for safety and efficacy.

Of the 2,806 participants in the group who received the first three doses of RTS,S, 2,444 received the fourth dose of RTS,S (87%). Given this was a trial setting, it may be optimistic to achieve this level of coverage in a routine program. In the trial, the main reason for not receiving the fourth dose was migration (Figure 3.4).[2]

For a variety of reasons, including the access to care and the size of the trial, it was not possible to detect any impact on the overall or malaria-related mortality. In fact a non-statistically-significant excess of deaths among the vaccinated group for both all-cause mortality and malaria-related mortality was observed. JTEG considers the closest surrogate for malaria-related mortality in the trial is severe malaria, but it is critical to evaluate the impact of the vaccine on mortality in routine program settings.

10.2 JTEG assessment of vaccine safety

Assessment of meningitis, febrile convulsions, and cerebral malaria

The meningitis signal was first observed among individuals who received three doses of RTS,S at ages 5-17 months. The signal persisted in the period more than 18 months after the initial vaccine course with or without a fourth dose. Although the excess of meningitis was nominally statistically significant, it is unclear whether or not the excess was causally related to the vaccine. Several aspects of the meningitis signal are currently unexplained. The cases of meningitis had a variety of aetiologies. The incidence of meningitis appeared to be very low in the control group, and more information on background rates of meningitis would aid interpretation. Most of the excess cases of meningitis came from two sites not in the meningitis belt. The possibility cannot be excluded that the signal may be due, at least in part, to a chance deficit of meningitis cases in the control arm. Continued monitoring of meningitis following vaccination is critical to understand whether excess in meningitis is causally related to the vaccine and if so, the mechanism behind it.

The trial demonstrated an increased risk of febrile seizures within seven days of vaccination among those vaccinated at age 5-17 months. In children in the younger age category an excess risk was apparent only after the fourth dose (when the children were older). These febrile seizures resolved without long-term consequence and are not unique to this vaccine.

JTEG noted an increase in cerebral malaria in the malaria vaccine older age category, although these cases comprised only a small proportion of all cases of severe malaria. This finding was in an unplanned subgroup analysis and its significance in relation to vaccination is unclear. The hypothetical concern is of changing the disease manifestation due to vaccination or because of delayed age of exposure. In the trial, participants were diagnosed with malaria and treated earlier than in routine health care settings, so the finding, if real, may not reflect what would be seen with

[2] Examples of vaccine coverage achieved for other vaccines (DTP3, MCV1, and MCV2) in countries in the WHO African Region may be found in Appendix 7.

wider deployment. The sub-group analysis showed that children with cerebral malaria had higher case fatality rates than other forms of severe malaria. An imbalance of cerebral malaria was not seen in children vaccinated in the younger age category.

Pharmacovigilance systems should be strengthened, not only for febrile seizures, cerebral malaria and meningitis, but for other potential adverse effects occurring at a frequency too low to have been detected in the Phase 3 trial. Such surveillance is also important because there is a relatively small database for the new adjuvant (AS01) in the vaccine. Because RTS,S/AS01 is a new vaccine with a relatively new adjuvant system, there should be surveillance for potential adverse effects, such as autoimmune disease.

GACVS has agreed to propose detailed protocols for safety studies of RTS,S if the vaccine is recommended for any large-scale use.

10.3 RTS,S/AS01 in the context of other malaria control measures

There are other proven strategies for malaria prevention and control. LLINs are one of the most cost-effective public health interventions. Sufficient coverage with existing interventions should be a priority and funds should not be diverted to vaccination from existing malaria control activities. RTS,S could represent a complementary tool to be used in conjunction with other control measures.

10.4 JTEG key conclusions and recommendations for SAGE/MPAC consideration

There is a need to evaluate initial introductions before wider scale-up is considered to address a number of issues that remain following the conclusion of the trial. The primary issues are:

- The extent to which the protection demonstrated in the Phase 3 trial could be replicated in the post-licensure phase because of the challenge of implementing four doses at the population level, including the need for new immunization contacts
- The safety signals of most concern (i.e. imbalances in meningitis and cerebral malaria) in the trial may be chance findings, but further evaluation is necessary when the vaccine is given to larger numbers of children
- The impact on mortality could not be assessed in the Phase 3 trial and as this is the main driver of the public health impact and cost-effectiveness of the vaccine, it is important to assess the mortality reduction following large-scale vaccination.

Based on the data from the Phase 3 trial, JTEG does not recommend the use of the malaria vaccine in the younger (6-12 weeks) age category. With respect to the older age category (5-17 months), JTEG recommends the initial introduction of 4 doses of the malaria vaccine in 3-5 distinct epidemiological settings in sub-Saharan Africa, likely at subnational level, to generate critical information on the issues described above (large demonstration projects). These settings should be selected such that

- they cover a range of moderate-to-high transmission settings, with at least one setting with strongly seasonal malaria transmission.
- it is possible to ascertain and diagnose cases of meningitis and severe malaria and record deaths.
- the population vaccinated should be of sufficient size to allow evaluation of the impact on mortality, probably through a phased introduction of the vaccine within the selected settings. It is likely that several hundred thousand vaccinated children will be included in each setting and that phased introduction would need to be randomized to ensure comparability of vaccinated and unvaccinated groups. Each initial introduction will be a large demonstration project.
- there should be high existing coverage of other proven malaria control measures including LLIN (or IRS), access to RDTs and ACT, and SMC in highly seasonal areas.

JTEG strongly recommends that WHO oversees the design and evaluation of these phased introductions and monitors the emerging findings. If appropriate, SAGE and MPAC may broaden recommendations on the basis of these emerging findings.

JTEG notes that it would be appropriate for WHO to recommend countrywide introduction if concerns about safety have been resolved, and if favourable implementation data become available, including high coverage of the fourth dose.

As JTEG recommends introduction in 3-5 moderate-to-high transmission settings, where there is a significant burden of malaria in the first year of life, it is important to vaccinate at a young age within the 5-17 month age range. There is no evidence that vaccine efficacy varied according to the month of age at which vaccination was started within this age category. In the phased introduction of the vaccine, JTEG recommends a three dose initial series of the malaria vaccine with a minimum interval between doses of four weeks, followed by a fourth dose at 15-18 months following the third dose. It is encouraged that the first dose be initiated as close as possible to age five months and the third dose be completed by nine months of age, if possible. Co-administration has been evaluated with measles and DTP-containing vaccines and is considered acceptable.

Prior to any phased introduction appropriate communication materials should be developed and disseminated with particular emphasis on the partial efficacy of the vaccine and the importance of the fourth dose. Messages should include the importance of maintaining usage of non-vaccine malaria preventive measures and the likelihood that febrile episodes in vaccinated children may still be due to malaria.

Research recommendations

There are currently no data to support a fifth dose. Therefore, evaluation of safety and effectiveness of a fifth dose could be included in the proposed phased introductions.

JTEG recommends monitoring of the emergence of vaccine-resistant strains following widespread use of the vaccine.

JTEG recommends that there is further exploration of alternative schedules, including schedules adapted to highly seasonal settings, and other strategies to improve the efficacy of the vaccine.

JTEG recommends an exploration of how to capitalize upon the new immunization contacts for general improvements in child health, including increasing coverage with other vaccines.

JTEG recommends that there is an evaluation of the malaria vaccine in the context of elimination, including studies evaluating administration and effectiveness against infection over a wide age range. A high priority geographic area for such an evaluation is South-East Asia in areas of artemisinin resistance.

Table 10.1: Risk/benefit assessment over median 48 months follow-up per child in those aged 5-17 months, based on Phase III trial results

	BENEFITS	RISKS	UNCERTAINTIES
3 dose schedule	VE2.5-SE clinical malaria: 26.2% (95%CI 20.8, 31.2)	<u>Identified risk</u> Excess of febrile convulsion after any of the first three doses (0.5/1000 doses within 7 days of vaccination) <u>Potential risk</u> Meningitis (numerical excess, no clear association with time since vaccination, biological model not well established, excess predominantly in only 2 of 11 sites)	Relevance of imbalance of cerebral cases, possibly due to chance
4 dose schedule	VE2.5-SE clinical malaria: 39.0% (95%CI 34.3, 43.3) VE2.5-SE severe malaria: 31.5% (95%CI 9.3, 48.3) VE2.5-SE all-cause hospitalization: 14.9% (95%CI 3.6, 24.8)	<u>Identified Risk</u> Excess of febrile convulsion after any of the first three doses (0.5/1000 doses within 7 days of vaccination) after fourth dose (2.0/1000 doses within 7 days of vaccination) <u>Potential Risk</u> Meningitis (numerical excess, no clear association with time since vaccination, biological model not well established, excess predominantly in only 2 of 11 sites)	Uncertain overall protection against severe malaria beyond trial period Beneficial overall effect on severe malaria is dependent on delivery of fourth dose Relevance of imbalance of cerebral cases, possibly due to chance

With the three-dose schedule, there was no significant protection against VE2.5-SE against severe malaria, or for VE 2.5-SE against all-cause hospitalizations in the 5-17 month age category.

Table 10.2: Risk/benefit assessment over median 38 months follow-up in those aged 6-12 weeks, based on Phase III trial results

	BENEFITS	IDENTIFIED RISKS	UNCERTAINTIES
3 dose schedule	VE 2.5 – SE clinical malaria: 18.2% (95%CI 11.4, 24.5)	None	NA
4 dose schedule	VE 2.5-SE clinical malaria: 26.7% (95%CI 20.5, 32.4)	Excess of febrile convulsion after fourth dose (1.6/1000 doses within 7 days of vaccination)	NA

With the three-dose or four-dose schedule, there was no significant protection against VE2.5-SE against severe malaria, or for VE 2.5-SE against all-cause hospitalizations in the 6-12 week age category.

Table 10.3: Evidence to Decision Table, GRADE_DECIDE Framework.

Question: Should 4 doses of RTS,S/AS01 given on a 0/1/2/20 month schedule to children aged 5 months be introduced into national immunization programs of countries with medium-high malaria transmission?	
Population: Children aged 5 months	
Intervention & Comparison: 4 doses of RTS,S/AS01 given on a 0/1/2/20 month schedule vs. no malaria vaccine	
Setting (if relevant): Countries with medium-high malaria transmission	
Decision domain	Summary of reason for decision
Quality of evidence (QoE) *Is there high or moderate quality of evidence* Yes ☐ No ☐ Mixed ✓	Quality of Evidence for benefits: High ✓ Moderate ✓ Low☐ Very Low ☐ Quality of Evidence for harms: High ☐ Moderate ☐ Low ✓ Very Low ☐
Balance of benefits and harms *Is there certainty that the benefits outweigh the harms?* Yes ☐ No ✓	Summary of benefits and harms of the Intervention. • There is partial efficacy against clinical and severe malaria, as well as all-cause hospitalization. • The benefits against malaria-related mortality and all-cause mortality are unknown. • There is an identified risk of febrile convulsions following vaccination. • There is a potential risk of meningitis following vaccination. • It is uncertain whether the imbalance of cerebral malaria cases seen in the trial is relevant. The benefits outweighed the risks for a 4-dose schedule in the clinical trial. 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.
Values and preferences *Is there confidence in the estimate of relative importance of outcomes and patient preferences?*	There is a strong public desire to reduce malaria cases, particularly severe and life-threatening malaria. There is increasing resistance to multiple injections at a single visit, suggesting new vaccination visits would be preferable.

Yes✓ No ☐	
Resource implications *Are the resources worth the expected net benefit?* Yes☐ No ☐ Unknown ✓	• The relative benefit/risk in the context of programmatic use is dependent upon adherence to four doses and additional information on mortality impact and vaccine safety. • Resources will be required for adding new vaccination visits (at least 1 for first 3 doses and an additional visit for fourth dose). • GSK has committed to at-cost (plus 5%) pricing. • Gavi will consider providing financial support. • Malaria prevention/control funds are allocated to proven interventions (e.g. LLIN, IRS, ACT)– there should be no diversion of funds from existing measures. • Other proven malaria preventive interventions are more cost-effective, hence the need to ensure that resources are not diverted from these to the vaccine. • Predictions of RTS,S/AS01 cost-effectiveness are comparable with other new vaccines, recommended for use by WHO.
Overall strength of recommendation: *Does the strength of recommendation adequately express the certainty?*	JTEG recommends use of RTS,S/AS01 in 3-5 settings in order to confirm implementation of a fourth dose and benefit/risk in the context of a routine immunization setting.
Implementation and considerations *How might implementation affect access to care and outcomes in disadvantaged and privileged groups?*	In many settings it will be challenging to implement and achieve high coverage of the four-dose schedule at the population level, particularly given the need for new immunization contacts. Close monitoring and evaluation of implementation will be needed. Good communication will be needed to ensure continued acceptability of RTS,S in the context of continued susceptibility to malaria after vaccination, as well as continued care seeking.
Research priorities *What are some of the additional research (surveillance, impact of immunization on disadvantage population, etc.) necessary after making a recommendation?*	• Pilot introductions are needed to assess the programmatic feasibility of implementing a 4-dose vaccine schedule, the impact of RTS,S vaccination on all-cause mortality, as well further assessment of the possible risks of meningitis and cerebral malaria. • There are currently no data to support a fifth dose. Therefore, evaluation of safety and effectiveness of a fifth dose could be included in the proposed phased introductions. • Monitoring of the emergence of vaccine-resistant strains following widespread use of the vaccine. • Further exploration of alternative schedules, including schedules adapted to highly seasonal settings, and other strategies to improve the efficacy of the vaccine. • Exploration of how to capitalize upon the new immunization contacts for general improvements in child health, including increasing coverage with other vaccines. • JTEG recommends that there is an evaluation of the malaria

	vaccine in the context of elimination, including studies evaluating administration and effectiveness against infection over a wide age range. A high priority geographic area for such an evaluation is South-East Asia in areas of artemisinin resistance.

11. Acknowledgements

JTEG would like to acknowledge the Partnership between the Malaria Vaccine Initiative at PATH and GSK. JTEG would also like to thank GSK for their data sharing and responsiveness to additional data requests important to the policy-making process. At WHO's request GSK/PATH published several methods papers outlining design aspects in detail. GSK provided WHO with all analyses requested, including statistical reports, and clinical study reports. GSK/PATH promptly published and publicly disclosed four comprehensive reports from the Phase 3 trial.

12. GRADE Tables

GRADE Table 1

Is there demonstrated short term efficacy of three doses of RTS,S/AS01 in preventing clinical malaria in children?

Population : 5-17 month old children living in malaria-endemic areas

Intervention: 3 doses of RTS,S/AS01 administered at least 4 weeks apart

Comparison: Placebo/Control vaccine

Outcome : Clinical malaria occurring within 12 months of completion of the primary series

What is the short-term efficacy of three doses of RTS,S/AS01 in preventing clinical malaria in children?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[2]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a high level of confidence that the true effect lies close to that of the estimate of effect on health outcome**
	Conclusion			**RTS,S demonstrates statistically significant vaccine efficacy against clinical malaria in the first 12 months following vaccination with three doses.**

[1] A multicenter efficacy trial was conducted at 11 sites in seven countries and included 8,922 participants assigned in the 5-17 month age category. It was a randomized, controlled, participant and observer-blinded trial (intervention and control vaccines differ in appearance, so study personnel who administered vaccines were aware of the treatment allocation. The unblinded vaccinators played no other part in the study)(NCT00866619). Vaccine efficacy against clinical malaria was estimated to be 32.9% (95%CI 26.3, 38.9) in the 12 months following a primary series (3 doses) of vaccine. A number of smaller Phase 2 studies also found statistically significant vaccine efficacy against infection and clinical malaria. The point estimates vary by follow up time given the waning efficacy even over the first year. Although only one RCT is the primary source of data, given the number of study subjects involved and the multi-center nature, it was determined not to downgrade.

[2] A large effect is noted in the first 6 months of follow up (VE=67.6%, 95%CI 63.8, 71.0), but it waned in the second 6 months of follow up to 38.9% (95%CI 33.2, 44.0).

GRADE Table 2

What is the short-term efficacy of three doses of RTS,S/AS01 in preventing severe malaria in children?

Population : 5-17 month old children living in malaria-endemic areas

Intervention: 3 doses of RTS,S/AS01 administered at least 4 weeks apart

Comparison: Placebo/Control vaccine

Outcome : Severe malaria occurring within 12 months of completion of the primary series

What is the short-term efficacy of three doses of RTS,S/AS01 in preventing severe malaria in children				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious[2]	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[3]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a high level of confidence that the true effect lies close to that of the estimate of effect on health outcome**
	Conclusion			**RTS,S demonstrates statistically significant vaccine efficacy against severe malaria in the first 12 months following vaccination with a primary series.**

[1]A multicenter efficacy trial was conducted at 11 sites in seven countries and included 8,922 participants assigned in the 5-17 month age category. It was a randomized, controlled, participant and observer-blinded trial (intervention and control vaccines differ in appearance, so study personnel who administered vaccines were aware of the treatment allocation. The unblinded vaccinators played no other part in the study)(NCT00866619). Vaccine efficacy against severe malaria was estimated to be 44.5% (95%CI 23.8, 59.6) in the 12 months following a primary series (3 doses) of vaccine.

[2]The number of severe malaria cases was very low in the trial; however here may be differences in the presentation of severe malaria among vaccinated individuals, as a numerical imbalance was seen for severe malaria in RTS,S-vaccinated subjects. It is uncertain how this will play out in larger scale use outside a trial setting. It was determined not to downgrade for these uncertainties, but they are noted.

[3]A large effect is noted in the first 6 months of follow up (VE=70.1%, 95%CI 49.0, 82.5), but it quickly wanes (see GRADE Table 3).

GRADE Table 3

Is there need for a fourth dose following immunization with the first three doses of RTS,S/AS01 in children to prevent severe malaria?

Population : 5-17 month old children living in malaria-endemic areas

Intervention: 3 doses of RTS,S/AS01

Comparison: Placebo/Control vaccine

Outcome : Severe malaria occurring at >12 months following the primary series.

Is there need for a fourth dose following immunization with the first three doses of RTS,S/AS01 in children to prevent severe malaria?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	Serious[2]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of effect on health outcome**
	Conclusion			**Among vaccinees who do not receive a fourth dose, in high transmission settings there is an increased risk of severe malaria following waning vaccine efficacy; therefore, a fourth dose is essential.**

[1]A multicenter efficacy trial was conducted at 11 sites in seven countries and included 8,922 participants assigned in the 5-17 month age category. It was a randomized, controlled, participant and observer-blinded trial (intervention and control vaccines differ in appearance, so study personnel who administered vaccines were aware of the treatment allocation. The unblinded vaccinators played no other part in the study)(NCT00866619). All participants were followed up for 32 months (approximately 30 months following the primary series). At study end, participants in this age category were followed up for a median of 48 months. Vaccine efficacy against severe malaria during the full trial period (2.5 months following 3rd dose to study end) in the absence of a fourth dose (i.e. primary series alone) was estimated to be -2.2% (-31.3, 20.4), suggesting that the primary course alone had no effect on the overall incidence of severe malaria. When efficacy/comparative incidence was analysed by time interval, efficacy against severe malaria was high in the first 6 months of follow up at 70.1% (95%CI 49.0, 82.5), but steadily declined to -47.9% (95%CI -134.6, 6.8) between 19-30 months after the primary series, and to -74.2% (95%CI -220.0, 5.2) between 31 months after the primary series and the end of the observation period. Thus, the apparent protective effect in the first 18 months being balanced by a rebound of cases in the period from 18 months to the end of the trial. Although only one RCT is the primary source of data, given the number of study subjects involved and the multi-center nature, it was determined not to downgrade. Among trial participants who received a fourth dose, the vaccine efficacy against severe malaria from the primary series to the end of the trial was 31.5% (95%CI 9.3, 48.3).

[2]Given the rapid reduction of vaccine efficacy/comparative incidence of a primary series as well as a fourth dose (see Background Paper), it is of interest what the effect of a fourth dose is on severe malaria beyond the trial conclusions, as well as whether subsequent doses (e.g. a 5th dose) are safe and efficacious. There are no data available to inform these questions.

GRADE Table 4

What is the risk of meningitis following vaccination with RTS,S/AS01 in children?

Population : 5-17 month old children living in malaria-endemic areas

Intervention: One or more doses of RTS,S/AS01

Comparison: Placebo/Control vaccine

Outcome : Meningitis due to all causes

What is the risk of meningitis following vaccination with RTS,S/AS01 in children?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	Very serious[2]	-2
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[3]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports limited confidence in the estimate of the effect on the health outcome.**
	Conclusion			**RTS,S/AS01 may or may not be causally-related to an increased risk of meningitis**

[1] A multicenter efficacy trial was conducted at 11 sites in seven countries and included 8,922 participants in the 5-17 month age category. It was a randomized, controlled, participant and observer-blinded trial (intervention and control vaccines differ in appearance, so study personnel who administered vaccines were aware of the treatment allocation. The unblinded vaccinators played no other part in the study)(NCT00866619). In the 20 months following the first dose, meningitis was reported as an SAE in 16 of the 5949 5-17 month old participants in the RTS,S group, and in 1 of the 2974 5-17 month old participants in the control group, a relative risk of 8.0 (95%CI 1.1, 60.3).

[2] There were a variety of etiologies, although in many of the meningitis cases no pathogen was identified. There was no clear temporal clustering, and most cases occurred at two study sites. The number of meningitis cases in the control group appears to be unusually low.

[3] The relative risk is large (8.0); however, given the other uncertainties, it was deemed not appropriate to upgrade the quality of the evidence.

GRADE Table 5

What is the risk of other (non-meningitis) serious adverse events following vaccination with RTS,S/AS01 in children?

Population : 5-17 month old children living in malaria-endemic areas

Intervention: One or more doses of RTS,S/AS01

Comparison: Placebo/Control vaccine

Outcome : Serious adverse events (non-meningitis)

What is the risk of other (non-meningitis) serious adverse events following vaccination with RTS,S/AS01 in children?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	Serious[2]	-1
		Inconsistency	None serious	0
		Indirectness	Serious[3]	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports limited confidence in the estimate of the effect on the health outcome.**
	Conclusion			**Febrile seizures are an identified risk of RTS,S/AS01 administered to children. The relevance of the imbalance of cerebral malaria cases in the RTS,S/AS01 group is uncertain. There is no evidence of an association to other SAEs[4].**

[1]A multicenter efficacy trial was conducted at 11 sites in seven countries and included 8,922 participants assigned in the 5-17 month age category. It was a randomized, controlled, participant and observer-blinded trial (intervention and control vaccines differ in appearance, so study personnel who administered vaccines were aware of the treatment allocation. The unblinded vaccinators played no other part in the study)(NCT00866619). In the 5-17 month group, between the first dose to the trial end, Serious Adverse Events (based on MEDRA preferred terms) were slightly less frequent in the RTS,S groups compared to the control group (R3R-24.2%, R3C-25.3%, C3C- 28.4%)(Table 6.1) and this remained so when malaria was excluded as an SAE (R3R-22.6%, R3C-23.7%, C3C- 26.4%). In the 5-17 month age category, the incidence of generalized convulsions (Brighton Collaboration diagnostic certainty level of 1 to 3) within the seven days following vaccination during the primary series was 1.04 per 1000 doses (95%CI 0.62, 1.64) in the RTS,S/AS01 groups (R3R + R3C) and 0.57 per 1000 doses (95%CI 0.19, 1.34) in the control group (C3C) (Table 4.3), a risk ratio of 1.8 (95%CI 0.6, 4.9). Following a fourth dose of RTS,S (R3R group), the incidence of generalized convulsions increased to 2.5 per 1000 doses (95%CI 0.9, 5.3) in the R3R group (Table 4.4). The incidence in the RTS,S group without a fourth dose of RTS,S/AS01 (R3C – received rabies vaccine as control fourth dose) was still 1.2 per 1000 doses (95%CI 0.3, 3.5), while the incidence in the control group (C3C) was 0.4 (95%CI 0.0, 2.3). Based on an unplanned subgroup analysis, there was an imbalance of cerebral malaria episodes in the RTS,S groups compared to the control group. In the 0-20 month time period, there were 24 episodes of cerebral malaria or cerebral malaria + anaemia in the RTS,S group and 6 episodes in the control group (2:1 randomization). In the 21 month to

study end time period, there were 9 episodes in the R3R group, 12 episodes in the R3C group, and 4 episodes in the C3C group (1:1:1 randomization).

[2]The trial did not have the power to detect more rare SAEs.

[3]For cerebral malaria, this was an unplanned subgroup analysis. Some cases of other coma-inducing diseases may have been misclassified as cerebral malaria.

[4]SAEs excluding meningitis, cerebral malaria and febrile seizures.

13. JTEG Membership and Terms of Reference

WHO Initiative for vaccine research/global malaria programme joint technical expert group (JTEG) on malaria vaccines entering pivotal phase 3 trials & beyond (established April 2009)

Terms of reference

JTEG provides advice to WHO on activities related to the development of malaria vaccines at or nearing the pivotal phase 3 trial stage. The specific responsibilities of the group are to provide recommendations on:

1. The clinical trial data necessary and desirable for evaluation of the public health impact of a malaria vaccine in malaria endemic countries
2. The design, conduct, analyses and interpretation of Phase 2, Phase 3 and Phase 4 trials of malaria vaccines.
3. The duration and nature of follow-up of participants in planned Phase 3 trials of malaria vaccines.
4. The minimum safety and efficacy data to be collected in clinical trials, and data on any impact of malaria vaccines on the immunogenicity of other vaccines, to enable evaluation by WHO for policy recommendations.
5. The evaluation of immunogenicity of malaria vaccines in Phase 3 trials and beyond, in particular with regard to possible development of surrogate markers for efficacy.

Composition

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Declarations of interest

All members completed a declaration of interest. 3 members reported the following interests:

Professor Fred Binka reported working with the Indepth-Network Malaria Clinical Trials Alliance (MCTA), a group which trains personnel and improves infrastructure at African clinical trials sites for conduct of clinical trials of malaria drugs and vaccines. Indepth/MCTA was funded by a $17 million grant from the Bill and Melinda Gates' Foundation (BMGF). The work of Indepth/MCTA included partnering with PATH Malaria Vaccine Initiative (MVI) for site strengthening of RTS,S/AS01 phase 3 clinical trial sites. BMGF are also the main funders of the phase 3 trial of RTS,S/AS01 through support to PATH MVI. In addition Professor Binka reported a research grant for the Indepth Network for Effectiveness and Safety Studies (INESS) for $28 million. This platform is intended to support Phase IV studies of antimalarial drugs. These interests were assessed as non-personal, non-specific and financially significant*.

Professor Malcolm Molyneux reported that he currently serves as Chair of the Independent Data Monitoring Committee for RTS,S/AS01 paediatric clinical trials, for which his institution receives a limited fee. This interest was assessed as non-personal, specific and not financially significant*.

Dr Janet Wittes reported that her institution has performed statistical consulting services for GSK for a study on asthma and another on cardiovascular diseases, totaling less than $50,000. The most recent consulting contract with GSK terminated in 2010. Her institution has also received funding for malaria vaccine-related statistical services from PATH Malaria Vaccine Initiative and from Seattle Biomed. None of this funding relates to the RTS,S malaria vaccine. These interests were assessed as non-personal, non-specific and financially significant*.

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* According to WHO's Guidelines for Declaration of Interests (WHO expert), an interest is considered "personal" if it generates financial or non-financial gain to the expert, such as consulting income or a patent. "Specificity" states whether the declared interest is a subject matter of the meeting or work to be undertaken. An interest has "financial significance" if the honoraria, consultancy fee or other received funding, including those received by expert's organization, from any single vaccine manufacturer or other vaccine-related company exceeds 10,000 USD in a calendar year. Likewise, a shareholding in any one vaccine manufacturer or other vaccine-related company in excess of 1,000 USD would also constitute a “significant shareholding”.

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15. List of Appendices

Available on web

Appendix 1. Clinical studies conducted with RTS,S/AS01 in subjects older than 17 months at first dose or with RTS,S/AS02

Appendix 2. Representative ITT Vaccine Efficacy Analyses

Appendix 3. Case counts and vaccine efficacy against clinical and severe malaria for Phase III trial (Mal-055)

Appendix 4. Results from long-term follow-up of Phase 2b trials of RTS,S/AS02 and RTS,S/AS01

Appendix 5. Hepatitis B immunogenicity and indication

Appendix 6. Incidence of malaria in the control group by site

Appendix 7. 2014 Estimated Vaccine Coverage for Select Vaccines, by Country in AFR

Related materials

Available on web

Additional Background Paper: "Programmatic Options for Implementation of Malaria RTS,S Vaccination Schedule for Young Children". Developed by WHO.

"Report on public health impact and cost-effectiveness of malaria vaccine RTS,S/AS01". This summary highlights key outcomes from a systematic comparison of estimates of the potential public health impact and cost-effectiveness from four modelling groups.

"Comparison of the cost effectiveness of LLINs, SMC, the RTS,S vaccine and RTS,S plus IPTi in African settings." MRC Centre for Outbreak Analysis and Modelling, Department of Infectious Disease Epidemiology, Imperial College London